

# Medical Writers' Circle

a series of articles

written by medical  
professionals about  
the management  
and treatment of  
Hepatitis C

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## The Future of Western Treatment for Hepatitis C

Despite current advances in treatment options, more effective and safer antiviral agents for hepatitis C are clearly still needed. About 40% of people who are infected with the hepatitis C virus (HCV) worldwide will not respond (viral clearance) long-term to our best current Western therapy in spite of compliance with full dosing and duration of therapy. Clearly, new therapies are needed to obliterate this global disease. A discussion of some of the treatments currently under investigation for hepatitis C is presented below.

### Therapies that Modulate the Immune Response

#### Interferon

Recently, polyethylene glycol molecules of different sizes have been attached to interferon at different sites forming "pegylated" interferon. This has allowed the development of biologically active interferon molecules. These molecules are not cleared by the kidneys as quickly and remain active in the body longer than standard alpha-2a and 2b interferon. The response rates of PEG IFN with ribavirin are in the 54-56% range according to the

recent licensing trials. Amgen, in coordination with Intermune Pharmaceuticals, may bring PEG IFN alfa con-1 to market as well. An albumin-interferon combination is being developed by Human Genome Sciences.

#### Vaccines

The development of a vaccine remains a challenge for several practical and scientific reasons. The hepatitis C virus can mutate to avoid detection by the body's immune system and the body's neutralizing antibodies (specific CD4 and CD8 T-cells) are not efficiently produced. The virus is only found in humans and chimpanzees and the virus replicates poorly in cell cultures in the laboratory. It is also important to note that the viral envelope proteins (E1/E2) are highly susceptible to mutation, making it difficult for antibodies to provide long-term protective immunity. This current scientific information highlights why vaccine development will be difficult. Chiron Corporation has published phase one trial data about an HCV vaccine in high risk patients demonstrating safety. Recent advances in recombinant protein technology, novel adjuvants, and DNA-based vaccines will play a

major role in providing new techniques for the development of vaccines. HCV antibody preparations are in clinical testing at this time to prevent recurrent disease after liver transplantation.

#### Products Derived from Thymus Extracts

Two thymus gland derivatives, thymosin fraction 5 and thymosin a-1, are cytokines that produce specific reactions in the cells of the body, including within the thymus gland itself. These thymus-derived proteins appear to be able to change a person's response to an HCV infection. A series of clinical trials using Thymosin a-1 have led to the approval of this medication in more than 20 countries for the treatment of patients with viral hepatitis C infection. Combination therapy with interferon is currently being studied in the US in a large clinical trial.

#### Targeting Specific Sites in the HCV Genome

The HCV genome has been studied extensively over the last 9 years. From these studies, we have been able to identify various HCV protein products involved in viral replication, translation, and

packaging. One enzyme, the HCV RNA-dependent RNA polymerase, is responsible for the replication of the entire HCV genome. It may be possible to develop drugs that target this enzyme and prevent the replication of the hepatitis C virus including a medication by AKROS Pharmaceutical. Other areas within the HCV genome are also likely targets for drug development. These are the

of action may be through blocking viral envelope stabilization. This approach may greatly reduce the ability of HCV to infect other cells and also to decrease the development of resistance. New ribavirin-like products such as vx497 may also have a role in expanding combination therapy for HCV. Mycophenolate mofetil is a new immunosuppressant that also blocks inosine mono-

to this and other regions of the virus and are being developed by ISIS Pharmaceuticals in cooperation with Elan Pharmaceuticals. Another approach uses a normal cell enzyme called a ribozyme. Ribozymes are RNA molecules that can be modified to attach to and break a specific RNA sequence such as the one the hepatitis C virus must make to reproduce (replicate) itself in order to cause disease.

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helicase enzyme, protease inhibitors, the internal ribosomal entry site (IRES), and the interferon sensitivity-determining region (ISDR). Despite the promise of these proteinase, helicase, and RNA-dependent RNA polymerase inhibitors, development of these agents is slowed by the lack of suitable cell culture or animal models, although recent advances in this will markedly speed up drug development! This means that it is difficult for drug developers to test the many thousands of possible compounds that must be developed before one is found that is effective and safe.

Alpha glucosidase inhibitors (DNJ and related compounds) are candidates to treat and suppress HCV replications due to their apparent ability to inhibit viral packaging although their mechanism

phosphate dehydrogenase (IMPDH), but appears to have a very weak effect on HCV replication. HCV attaches to liver cells and other cells through the CD81 receptor. The development of molecules that block the attachment of the virus to the human cell would block viral entry. This product could work alone or in combination with other medications to aid in viral suppression or clearance. Analogues to ribavirin, levovirin and a prodrug of ribavirin, targeting the infected liver cells are being developed by ICN Pharmaceuticals to advance HCV therapy

Although there are many variations of the hepatitis C virus (HCV), one part is the same in all variations. This part is called the 5'untranslated region, or UTR. Scientists have learned how to add molecules, called "antisense" molecules,

Recently, synthetic ribozymes have been developed to specifically target and break up the 5'UTR portion of the HCV RNA. These synthetic anti-HCV ribozymes have been tested in cell cultures and in animal by RPI Pharmaceuticals. These additions cut existing viral copies of HCV and prevent the virus from replicating. Early clinical trials have recently been started to evaluate the safety of this new approach in humans. There have been no serious side effects in the animals tested. Ribozymes are currently in phase I human studies for HCV.



# Medical Writers' Circle

*is a program of the Hepatitis C Support Project.*

The Mission of the Hepatitis C Support Project is to offer support to those who are

affected by the hepatitis C Virus (HCV) and HIV/HCV coinfection.

Support is provided broadly, through information and education, as well as access to support groups. The (Project) seeks to serve the HCV community as well as the general public.

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