

# Medical Writers' Circle

a series of articles

written by medical

professionals about

the management

and treatment of

Hepatitis C

**Paul Pockros, M.D.**

Center for Liver Diseases  
at Scripps Clinic,

La Jolla, California.

## FUTURE HCV THERAPIES

**C**hallenges facing our current treatment of HCV include lack of efficacy in genotype 1 individuals (who represent a majority of U.S. HCV infections), combination therapy's toxicity, the expense and difficulty of therapy and the poor reception of these treatments by many patients. The development of new hepatitis C antiviral agents is critical to our management of this epidemic disease. A number of approaches are under investigation including long-acting interferons, immunomodulators, anti-fibrotics, specific HCV-derived enzyme inhibitors, drugs that either block HCV antigen production from RNA or prevent normal processing of HCV proteins, and other molecular approaches to treating HCV; such as ribozymes and antisense oligonucleotides.

### LONG-ACTING INTERFERONS

The poor sustained responses seen in three times a week dosing of interferon- $\alpha$  (IFN) may be related to the inability of this regimen to maintain therapeutic IFN levels and thereby exert sustained viral pressure. The creation of pegylated interferons (PEG-IFN) has produced compounds with prolonged absorption, decreased renal clearance and lack of antibody production. These compounds have a longer half-life compared to regular interferons and thus may be given once weekly with excellent therapeutic

levels. A recent study demonstrated sustained virologic response rates (SVRs) of 35% in HCV patients who were previously untreated. The adverse events and laboratory abnormalities associated with PEG-IFN appear to be similar to those seen with IFN therapy and significantly less than those seen with combination therapy. PEG-IFN appears to offer improved efficacy in cirrhotic patients as well. Two large multi-center phase III trials recently confirmed that both peginterferons are better than standard IFN. The improved efficacy and ease of use of these drugs will almost guarantee their substitution for our current IFNs.

The results of a large (n=1,530), multicenter, randomized trial of PEG interferon alfa-2b (PEG Intron) plus ribavirin compared to Rebetron have now been published. This study clearly showed that there was an effective dosage of PEG Intron which is weight-based (1.5mcg/kg) that is more effective than Rebetron in genotype 1 low viral load patient (< 2 million copies). The lower dosage of PEG Intron given at 0.5mcg/kg was no different than Rebetron. No dosage of PEG Intron combination was more effective than Rebetron in genotype 1 (high viral load > 2 million copies) or genotype 2 or 3 patients. The study used a fixed dosage of ribavirin (800 mg) rather than weight-based dosing, so we do not know if ribavirin should be given as a weight-based regimen

(as we do with standard IFN alfa-2b) or a fixed lower dosage of 800 mg. As well, all patients were treated for 48 weeks so we do not know if genotype 2,3 patients may be successfully treated for only 24 weeks.

A second trial (n=1,121) of combination pegylated (40kD) interferon alfa-2a (PEGASYS) in combination with ribavirin given at 1,000 to 1,200 mg showed improved efficacy for both genotype 1 (46% vs. 37%, P=0.016) and genotypes 2,3 (76% vs. 61%, P=0.008) over Rebetron. These results have been presented in abstract form at a major meeting but have not yet been published. No head-to-head trial of the 2 compounds has been performed so it is difficult to directly compare them to one another.

PEG Intron and ribavirin (Rebetrol) have both been FDA approved and are available for clinical use. PEGASYS is not expected to be FDA approved until the second half of 2002. The retail price of combination PEG Intron and ribavirin for 48 weeks will be approximately \$25,000.00.

### IMMUNOMODULATORS/ANTI-FIBROTICS/ CYTOPROTECTIVE AGENTS

A number of immunomodulators, anti-fibrotics and cytoprotective agents which might be helpful blocking liver cell injury caused by HCV are currently under study. Many of these drugs have

been given with interferon, growing on earlier lessons learned from ribavirin, which was ineffective when tested alone. A histamine analogue, which appears to improve efficacy of IFN looks promising and a trial of the drug in combination with long-acting IFN is currently underway in Europe.

Interferon gamma-Ib has been shown to be effective in reversing fibrosis (scar formation) of the lung in patients with idiopathic pulmonary fibrosis. It is now being studied in patients with advanced fibrosis or cirrhosis due to HCV to

protease enzymes are aspartase based, whereas the HCV protease is serine based and therefore HIV protease inhibitors have no effect on HCV replication. As with HIV, the use of viral enzyme inhibitors in HCV therapy would likely cause drug-resistant mutations.

There are 3 likely target enzymes: the HCV protease, the HCV helicase, and HCV polymerase enzymes. Each has a crucial step in virus replication. The crystal structure of the hepatitis C N53 protease enzyme was published in 1996; however, an effective inhibitor has

chronic infection. A number of groups have created vaccines utilizing CTL epitopes and plan to use them as potential HCV therapy. None are in human trials yet.

## MOLECULAR APPROACHES TO HCV THERAPY

### Antisense Oligonucleotides

Antisense drugs block the synthesis of disease-causing proteins by preventing translation of mRNA. In the case of HCV, an antisense oligodeoxynucleotide directed against a specific HCV sequence effectively inhibits viral

viral translation and expression in the host cell.

The possible synergistic effects of the combined active ribozyme preparation and type 1 interferon (IFN; Inergen®) are currently being studied in a phase 2 trial in the U.S.

### SUMMARY:

Our current state of the art chronic HCV therapy is at best, adequate for a minority of patients (non-1 genotypes), in addition to being cumbersome, toxic and difficult to administer. For these and other reasons, physician and patient acceptance has been limited and only a few percent of infected individuals receive treatment. Pegylated interferons have been introduced this year offer improved efficacy and ease of use. The combination of PEG-IFN with ribavirin will be the standard of care for treatment of HCV for the next 3-5 years.

We are at the leading edge of new therapeutic approaches to HCV including antisense therapy, hammerhead ribozymes, and specific enzyme inhibitors such as RNA polymerase. When such agents become available, we may treat HCV as an infectious disease, rather than a liver disease. Ultimately, we need oral drugs that are easy to take, non-toxic, inexpensive and efficacious across all HCV genotypes and subtypes.

*The ideal targets for new drug therapies are viral enzymes critical to HCV*

*replication. This targeting strategy has been quite successful in HIV suppression*

*and serves as a logical model for HCV drug development.*

determine if it will reverse or halt the progression of their disease.

Other possibly useful drugs under study are IMPDH (inosine monophosphate dehydrogenase) inhibitors, which have anti-inflammatory and antiviral activities similar to ribavirin and thymosin-alfa1, an immunomodulator to be studied in combination with peg-interferon alfa-2a. Less promising drugs in prior trials have been IL-12, IL-10, Ursodiol, glycyrrhizin, and combination IFN with amantadine or rimantadine.

## HCV ENZYME INHIBITORS/ PROTEIN PROCESSING INHIBITORS:

The ideal targets for new drug therapies are viral enzymes critical to HCV replication. This targeting strategy has been quite successful in HIV suppression and serves as a logical model for HCV drug development. Unfortunately, the HIV

not been produced. NS4A and NS43, other HCV proteases, are additional targets.

The polymerase enzymes will be the first inhibitor drug target in humans. A number of groups have described the three-dimensional structure of these enzymes and have inhibitors in animal studies. The first human trials (phase 1) are currently underway.

### T-CELL IMMUNOTHERAPY:

Cytotoxic T lymphocytes (CTL) play an important role in viral clearance and subsequent humeral immunity in hepatitis B patients. In a similar fashion, it is thought a CTL response contributes to HCV clearance in those few individuals that have spontaneous resolution of infection. A vigorous, polyclonal CTL response is seen in both chimpanzees and humans who clear infection, whereas HCV-specific CTL's failed to develop in those with

gene expression. This construct concentrates in the liver when given by intravenous infusion. A number of HCV-infected patients have received this antisense oligonucleotide infusion in a phase I/II trial at our center to demonstrate safety and tolerability. The efficacy of the compound is currently in a phase 2 trial.

### Ribozymes

Stabilized Ribozymes, small catalytic RNA molecules directed against a specific region (5'-UTR) of the hepatitis C virus genome (that is highly conserved across the various genotypes of HCV), are currently being tested as novel therapy for HCV infection. The 5'UTR region of viral RNA functions as an internal ribosomal entry site (IRES) and participates in the HCV genome translation within the cell to produce infective virions. A ribozyme directed to this viral RNA region might effectively block the