

Medical Writers' Circle

February • 2006

a series of articles
written by medical
professionals about
the management
and treatment of
hepatitis C

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Future Therapies for Hepatitis C

The U.S. Centers for Disease Control and Prevention predict that HCV-related mortality and attendant health care costs will double or triple over the next 10 to 20 years. Importantly, an estimated 20% of these patients have or will develop cirrhosis, and the annual risk of developing hepatocellular carcinoma (HCC) is 1% to 4% among patients diagnosed with chronic HCV-related cirrhosis.¹ Despite current advances in treatment options about 50% of people who are infected with the hepatitis C virus (HCV) worldwide will not respond, as defined by viral clearance, to our best current Western therapy (pegylated interferon and ribavirin) in spite of compliance with full dosing and duration of therapy.

Clearly, new therapies are needed to treat chronic hepatitis C. Within the next 10 to 15 years, new medications to treat HCV will likely become available including new types of interferon, alternatives to ribavirin, specific HCV inhibitors and newer immunotherapies. This article will focus on those drugs that have progressed through phase II clinical trials and that might be available for treatment of the general population within the next 5 - 10 years.

Hepatitis C Life Cycle

Hepatitis C is an enveloped, single-stranded RNA virus belonging to the Flaviviridae family. Viral strains split into a number of groups called genotypes (genotypes 1 through 6) which are additionally divided into a large number of subtypes notated by lower case letters (subtypes 1a, 1b etc.). There are six major genotypes in the world industrialized nations. Genotype 1 is the most prevalent in the U.S. followed by genotype 2 and 3.

HCV mainly infects hepatocytes (liver cells) and enters the cell via a receptor complex through a mechanism that remains unclear. In the cell cytoplasm, the virus is uncoated and releases the single-strand genome. The HCV viral genome is a messenger within the cell that binds to internal ribosome entry site (IRES) located in the 5' noncoding region. The single open reading frame is translated into a polyprotein (approximately 3000 amino acids, depending on the HCV genotype), which is additionally cleaved (sliced) by the host cellular and viral proteinases into structural and nonstructural proteins. The structural proteins include the core protein and E1 and E2 envelope proteins, which are glycoproteins. The nonstructural proteins include NS2, NS3 (which bears serine proteinase, helicase, and NTPase activi-

ties), NS4A, NS4B, NS5A (which regulates RNA replication), and NS5B (the RNA-dependent RNA polymerase). Each of these viral proteins is a potential target for therapy.

Replication takes place in the replication complex, which is modified to increase the chemical reaction by RNA-dependent RNA polymerase and uses positive-strand genomic RNA templates to synthesize negative strand intermediates that, in turn, serve as the templates for the production of new positive-strand RNAs, which can either be encapsidated to form new viruses that are released into the blood stream or be used as messenger RNAs for additional viral protein production.²

Agents that interfere with any step in the replication process can potentially be developed as therapies for hepatitis C.

New Interferons

New types of interferon are currently being developed and are expected to yield more potent antiviral effects and, eventually, more potent immunomodulatory effects, with improved pharmacokinetic and pharmacodynamic properties with, hopefully, better tolerability. Non-alfa interferons and oral interferon inducers such as Toll-like receptor agonists are also being studied.

Infergen (IFN alfacon-1, Consensus Interferon) (Valeant Pharmaceuticals), is currently FDA approved as a single agent and has been used in combination with ribavirin for some time. This interferon, a synthetic recombinant type 1 interferon containing 166 amino acids, is a consensus interferon (CIFN)⁵ created by scanning the sequences of many natural alpha interferons and assigning the most frequently observed amino acid in each corresponding position to a recombinant molecule. The intrinsic antiviral activity of this interferon appears to be greater than that of other standard interferons (interferon alfa-2a and alfa-2b) by both in vitro assays and human studies. Consensus interferon is currently in a large phase III licensing trial used with ribavirin to treat patients who have not responded to a previous course of pegylated interferon and ribavirin therapy. The long-term future use of consensus interferon will depend on the details of this phase III study and on the development of a pegylated form or another delivery system that can compete with the current weekly dosing of pegylated interferon and is expected to show improved response rates in the non-responder population. *Albupheron* (Human Genome Sciences), currently in phase II studies, is an interferon molecule fused to an albumin moiety. Interim results in naïve patients with chronic hepatitis C and in patients who did not respond to a previous course of interferon therapy reported that the drug is well-tolerated and has a prolonged half-life that allows dosing at intervals of 2 to 4 weeks.^{3,4} Current clinical trials are assessing whether bimonthly or monthly injections in combination with ribavirin could yield equivalent or

even better results than the current standard of care with weekly pegylated interferon. Results will also have to be balanced against the toxicity profiles of these drugs, which may improve with less frequent dosing. Phase II study results are expected in Spring, 2006 and phase III development is expected towards the end of 2006.

Ribavirin-Like Medications

The principal side effect of ribavirin is hemolytic anemia which is associated with dose reductions and treatment discontinuations that result in treatment breakthroughs and relapses after therapy.^{6,7,8} An alternative is needed that has the same antiviral effect as ribavirin, but without ribavirin induced hemolytic anemia. The development of such ribavirin-like molecules is hampered by the fact that the antiviral mechanisms of ribavirin remain poorly understood.

Viramidine (Valeant Pharmaceuticals) is an amidine version of ribavirin that is converted into ribavirin by adenosine deaminase, which is found in hepatocytes (liver cells). Viramidine is preferentially taken up in the liver and serves as a prodrug for local ribavirin delivery to the major site of HCV replication rather than to red blood cells.^{9,10} As a result the incidence of hemolytic anemia should be dramatically reduced.

In phase I studies in healthy volunteers, viramidine was well-tolerated, well-absorbed after oral administration, and rapidly and extensively converted to ribavirin, with subsequent transformation of ribavirin into its active metabolites. An open-label, active-control, multicenter, 48-week phase II study of combination therapy

with pegylated interferon alfa-2a plus viramidine or ribavirin has been completed. In this trial, 180 treatment-naïve individuals with chronic HCV infection were randomly assigned to receive either viramidine 400, 600, or 800 mg twice daily or ribavirin 1000 or 1200 mg/day in divided doses (accordingly to body weight lower or higher than 75 kg) in combination with pegylated interferon alfa-2a µg/week. Patients with genotype 2 or 3 were treated for 24 weeks and patients with genotype 1, 4, 5, or 6 were treated for 48 weeks.¹¹ Sustained virological response (undetectable HCV RNA six months after the end of treatment) was comparable in the viramidine 600 mg group as opposed to the ribavirin group (37% vs. 44% respectively). The same result was also found in subanalyses done by genotype. Significantly fewer patients experienced anemia in the viramidine groups than in the ribavirin group (4% vs. 27%; $p < .001$). The incidences of severe anemia, defined by a hemoglobin level lower than 10 g/dL, were only 0%, 2%, and 11% in the viramidine 400, 600, and 800 mg twice daily groups, respectively, and 27% in the ribavirin group. Other adverse events were similar in nature and frequency between treatment groups. The 600 mg twice daily dosage of viramidine was chosen for evaluation in ongoing phase III studies in combination with pegylated interferon alfa-2a and alfa-2b.

SPECIFIC HCV INHIBITORS

The recent determination of the 3D structure of various functional viral elements (including HCV proteins and genome structures), and the development of in vitro

assays to assess the antiviral potency of molecules targeting these elements, has made it possible to screen and develop specific small-size inhibitor molecules.^{2,12} Currently, the principal targets of new antivirals are the HCV IRES, the HCV NS3 serine proteinase, and the HCV RNA-dependent RNA polymerase. However, any functional HCV structure and any step of the life cycle can theoretically be inhibited, and new classes of inhibitors are likely to appear in the future.

Internal ribosome entry site inhibitors

The IRES is a functional stem-loop RNA structure located in the 5' noncoding region of the HCV genome that also spans the first core-coding nucleotides and drives HCV polyprotein translation. Inhibiting IRES function should therefore block the formation of the translational complex involving the ribosomal subunits and cellular proteins and inhibit translation of the HCV polyprotein. To date, only nucleic-acid based strategies have been used with essentially three classes of IRES inhibitors: antisense oligodeoxynucleotides, ribozymes, and small-interfering RNAs (siRNAs).

Antisense oligonucleotides are unmodified or chemically modified single-stranded DNA or RNA molecules designed to prevent the translation of viral RNA.¹³ Specific binding between an antisense oligonucleotide and its target RNA results in a hybrid RNA molecule that is subsequently degraded by the cellular enzyme RNase H.^{13,14}

ISIS 14803 (Isis Pharmaceuticals) is a 20-base phosphorothioate antisense oligodeoxynucleotide that inhibits HCV replication and protein expression in cell cultures

and mouse models. However, ISIS 14803 reduced HCV viral load only moderately in a small number of patients recently who experienced a simultaneous aminotransferase flare. Investigators were seeking to determine whether this drug possessed direct antiviral effects or worked through an indirect mechanism (i.e., immunomodulation via its GC motifs) when development was discontinued.

Ribozymes are catalytic RNA molecules that bind to and cleave specific RNA sequences. Heptazyme is an IRES-specific ribozyme that has also been investigated in phase II trials. However, development of this agent was halted because of toxicity in primates.

NS3 serine protease inhibitors

A nonstructural protein encoded by the HCV genome, the functional NS3 serine protease, combined with its cofactor NS4A, offers several target sites to small antiviral molecules [69], for instance, the catalytic site or the substrate binding site. The 3-dimensional structures of these domains have been determined.

BILN 2061 (Boehringer-Ingelheim) is an NS3 protease inhibitor targeted to HCV genotype 1 that profoundly and specifically inhibits HCV replication in vitro. However, This agent will not be developed because of myocardial toxicity in animal studies.¹⁵

VX-950 (Vertex Pharmaceuticals) is another NS3 protease inhibitor that targets the catalytic site of the enzyme. It belongs to a different class of drugs than *BILN 2061* and has different mechanisms of action and pharmacokinetic properties. In animal studies, the initial doses of *VX-950* and *BILN 2061* yield

similar levels of protease inhibition when administered in fixed multiples of their 50% inhibitory concentrations (IC50s). However, after 12 to 15 days, *VX-950* shows better efficacy than *BILN 2061*, producing more than 1-log greater drops in the HCV replicon system.¹⁶ A recent placebo-controlled phase Ia clinical trial found that oral *VX-950* is bioavailable and yields desired blood concentrations when administered at or above the middle range of the doses tested.¹⁷ Data also showed that liver exposure to *VX-950* was 113 times higher than the IC50 determined in a replicon-based assay. The drug was well-tolerated at all doses and was not associated with any serious adverse events.

The results of a trial were recently presented in which *VX-950* was administered at three dosages over 14 days in patients with HCV genotype 1 infection who had not responded to previous IFN alfa therapy. All treatment groups achieved an average 3- to 4-log HCV RNA drop within the first hours or days of treatment. Patients receiving 750 or 1250 mg twice daily experienced a rebound of HCV RNA load of about 1 log at the end of 14 days of administration; the mechanism of this effect is not yet known. However, no such relapse was seen in the patients receiving 750 mg three times daily. Patients had different HCV kinetic profiles, but most showed a biphasic decline in viral replication that included a second slope of viral decrease. *VX-950* was well-tolerated, and no major side effects were reported.

Interim data from a recent phase 1b randomized, blinded, placebo controlled study of 20 treatment naïve patients given the combination of *VX-950* (750 mg) and pegylated interferon (8 patients),

VX-950 alone (8 patients) or pegylated interferon (4 patients) for 14 days was released. Patients receiving the combination of *VX-950* and pegylated interferon achieved a median 5.5 log₁₀ (300,000-fold) reduction compared to a median 4.0 log₁₀ reduction in HCV RNA for the group that received *VX-950* monotherapy, and a median 1.0 log₁₀ reduction in HCV RNA for the group that received pegylated interferon monotherapy.

VX-950 currently appears to be one of the most promising of the specific HCV inhibitors in clinical development. The role of HCV resistance in the observed relapses on therapy has been established and, together with the mid- and long-term safety profiles, will determine the utility of this drug in the treatment of chronic hepatitis C. In December 2005, *VX-950* received Fast Track designation from the U.S. Food and Drug Administration.

Several companies have developed other NS3 protease inhibitors that target various sites of the enzyme and that are in early clinical development. SCH 503034 (Schering-Plough) is one of these that has been shown to have potent anti-HCV activity in preclinical studies. In a phase I study, the drug was found to be readily bioavailable when administered orally and was well-tolerated in doses of up to 800 mg.¹⁸ In a dose-ranging study of 61 patients who had previously failed peg-IFN therapy, patients treated with SCH 503034 1200 mg/day in three divided doses experienced a greater than 2 log₁₀ decrease in HCV RNA from baseline after 14 days.¹⁹ Adverse events were similar to those reported in patients receiving placebo. Phase II clinical trials of SCH 503034 will commence in 2006. In January

2006, SCH 503034 received Fast Track designation from the U.S. Food and Drug Administration.

NS5B RNA-dependent RNA 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.²⁰

Valopicitabine (NM283, Idenix Pharmaceuticals) is a nucleoside analog that targets the NS5B polymerase active site. A double-blind, randomized, phase I dose escalation clinical trial evaluated the safety, pharmacokinetics, and antiviral activity of valopicitabine in patients with chronic HCV infection who were treated for 15 days and followed for 2 weeks.²¹ All patients were infected with HCV genotype 1 and had not responded to previous IFN-based therapy (87%) or were untreated (13%). Patients were randomly assigned to receive valopicitabine 50, 100, 200, 400, or 800 mg once daily, 200 mg twice daily, or placebo. Two additional groups were created to evaluate titrated dosages up to 800 mg/day with a goal of optimizing gastrointestinal tolerance of the higher doses. Each of the eight active treatment groups included 12 patients, 10 receiving valopicitabine (9 in one group) and 2 receiving placebo. A dose-related, consistent but moderate viral load reduction was evident after 15 days of treatment. Patients receiving the highest overall dose exposure (800 mg/day) achieved a mean viral load reduction of 1.2 log₁₀. Although side effects were generally mild, an antiemetic (anti-vomiting medicine) was

required for some patients during the first few days of dosing.

The safety, pharmacokinetics, and antiviral efficacy of valopicitabine alone and in combination with PEG-IFN alfa-2b has also been studied in a 4-week randomized, phase IIa trial. Thirty treatment naïve patients with HCV genotype 1, a baseline viral load greater than $5 \log_{10}$ copies/mL, and aminotransferase levels less than 5 times the upper limit of normal were included. Patients received valopicitabine monotherapy (n=12) or valopicitabine plus pegylated IFN alfa-2b (n=18) for 3 months. Interim results in the patients receiving combination treatment included rapid reductions in HCV RNA levels and an apparent additive antiviral effect of pegylated IFN and valopicitabine.²²

In a phase IIb trial, the antiviral efficacy of valopicitabine was evaluated in 173 nonresponders to combination peginterferon plus ribavirin therapy.²³ Compared to subjects treated with peginterferon alfa-2a plus weight-based ribavirin, combination therapy with valopicitabine (400 mg/d ramped to 800 mg/d or 800 mg/d) plus peginterferon alfa-2a produced a significant improvement in the number of patients showing an early virologic response. Administration of peginterferon plus valopicitabine did not alter the pharmacokinetics of the latter.²⁴

In another phase 2b trial, the antiviral efficacy of valopicitabine in combination with pegylated interferon with a target enrollment of 175 treatment naïve patients is underway. All patients will be treated with valopicitabine in combination with pegylated interferon alfa-2a (Pegasys), 180 ug per week. This on-going 48-week clinical trial includes five randomized treatment arms:

(1) Pegylated interferon beginning on Day 8 plus valopicitabine ramping up from 400 mg to 800 mg beginning at Day 29; (2) valopicitabine 200 mg beginning on Day 1 plus pegylated interferon beginning on Day 8; (3) valopicitabine ramping up from 400 mg to 800 mg beginning on Day 1 plus pegylated interferon beginning on Day 8; (4) valopicitabine 800 mg beginning on Day 1 plus pegylated interferon beginning on Day 8; (5) valopicitabine 800 mg plus pegylated interferon, both beginning on Day 1. Interim 4-week data found that the four treatment arms that included valopicitabine in combination with pegylated interferon during the first four weeks all produced proportionally greater suppression of HCV RNA compared to the arm that include pegylated interferon alone. The mean reduction in HCV RNA levels was greater than or equal to $4 \log_{10}$, or 99.99 percent.

Numerous companies are also developing nucleosidic-nucleotidic and nonnucleosidic inhibitors of the HCV RNA-dependent RNA polymerase, some of which could enter clinical evaluation soon.

IMMUNE THERAPY

Nonspecific immunomodulatory agents

Various nonspecific immunomodulatory agents have been administered to patients with chronic hepatitis C with little success to date.

Thymosin is a thymic extract thought to promote T-cell maturation, stimulate the production and release of several cytokines, and increase the activity of natural killer (NK) cells. Thymalfasin (thymosin alfa-1, SciClone) is currently being evaluated in combination with pegylated IFN

alfa-2a in patients unresponsive to standard therapy. Two large randomized trials, now fully enrolled in the United States, are comparing pegylated IFN alfa-2a, ribavirin with and without thymalfasin in patients with and without cirrhosis. In December, 2005 data from the first study of patients without cirrhosis demonstrated only modest improvement in treatment outcome when thymosin was used in combination with pegylated interferon, but the difference was not statistically significant. Data from the second clinical trial of triple combination therapy (thymosin, pegylated interferon and ribavirin) is expected in May 2006.

Pan caspases are a group of cellular proteases that are involved in the inflammation and destruction of cells. IDN-6556 (Pfizer) is a pan caspase inhibitor in clinical trials for the treatment of hepatitis C induced liver disease and liver transplantation. IDN-6556 recently completed phase II clinical studies for the treatment of hepatitis C. The results showed that the drug was well-tolerated and that there were improved markers of liver disease in the patients who were treated. Phase III studies will commence in 2006.

CONCLUSIONS

Chronic hepatitis C is a major contributor to global liver-related morbidity and mortality. Although important advances in anti-HCV treatment have been made in recent years, many patients still do not clear infection. Several new drugs are in various stages of development to treat chronic HCV infection and to improve outcomes. New, more potent IFNs and alternatives to

ribavirin, such as viremagine, are being evaluated clinically. Novel therapies, based on specific inhibitors of HCV replication, as well as immunomodulatory approaches based on therapeutic vaccines, are emerging. These new therapies may improve the results of hepatitis C therapy. However, documentation of the durability of a sustained virological response and approval of these therapies is years away, and treatment algorithms will need to be redefined in the context of these advances.

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Medical Writers' Circle

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