

AASLD: Investigational Antiviral Therapies for Hepatitis C



Liz Highleyman

Among the topics that generated the most interest at this year's annual meeting of the American Association for the Study of Liver Diseases (AASLD), held October 27-31 in Boston, was the prospect of new therapies for chronic hepatitis C virus (HCV) infection.

STAT-C

Several investigational agents making their way through the development pipeline not only have the potential to incrementally increase the likelihood of sustained virological response, but also represent a paradigm shift in how hepatitis C is treated.

Current interferon-based therapy works by stimulating the body's natural immune response to the virus. In contrast, various novel agents – now collectively known as *specifically targeted antiviral therapy for HCV*, or “STAT-C” – directly attack HCV. Much like some of the drugs used to treat HIV, several experimental compounds inhibit HCV protease or polymerase, two enzymes the virus

needs in order to reproduce.

Speaking at a satellite symposium on STAT-C sponsored by Vertex Pharmaceuticals, hepatology expert Ira Jacobson predicted that this new approach “will revolutionize the way we treat chronic HCV infection,” offering the promise of “significantly higher rates of efficacy and significantly lower durations of treatment.” However, as with HIV therapy, the success of treatment with antiviral agents is limited by the development of drug resistance.

TELAPREVIR

One of the investigational agents generating the most excitement is telaprevir (VX-950), an oral HCV protease inhibitor being developed by Vertex. In the October 2006 issue of *Gastroenterology*, Henk Reesink and colleagues reported that in a Phase Ib study, telaprevir potently suppressed HCV replication in genotype 1 patients over 14 days when used alone (maximum 4.4 log decline in the 750 mg thrice-daily arm) or in combination with pegylated



IN THIS ISSUE

AASLD:

Investigational Antiviral Therapies for Hepatitis C.....1

Healthwise:

Your Rights as a Patient.....3

Donor Registry:

Alaska.....6

interferon (5.5 log decline). Researchers presented follow-up data at AASLD (abstract 1142) showing that all 15 participants who initially received telaprevir, with or without pegylated interferon, and continued on standard therapy with pegylated interferon plus ribavirin had undetectable HCV after 24 weeks of follow-up. Similarly, in a separate presentation, Maribel Rodriguez-Torres and colleagues (abstract 927) reported that eight of 12 patients enrolled in a 28-day study of triple therapy with telaprevir, pegylated interferon, and ribavirin still had undetectable HCV RNA after stopping telaprevir and continuing standard therapy for 24 weeks.

Tara Keiffer of Vertex (abstract 92) presented data from an analysis of resistance muta-

continued on page 2

AASLD: ANTIVIRALS

continued from page 1

tions in the 14-day study. Using a highly sensitive assay, researchers analyzed the presence of HCV variants with mutations previously identified as conferring low-level (V36M/A, T54A, R155K/T) or high-level (A156V/T and 36/155) resistance to telaprevir *in vitro*. Among the eight patients assigned to receive telaprevir monotherapy, four experienced virological breakthrough or a plateau response and showed evidence of predominant HCV variants with V36M/A and R155K/T mutations by Day 14. The other four experienced continuous HCV RNA decline, even though two developed viral variants with the A156V/T mutation. The researchers concluded that telaprevir produced a “sharp reduction in wild-type virus,” allowing resistant variants to emerge. Patients who experienced virological breakthrough and switched to pegylated interferon plus ribavirin achieved undetectable viral load within 24 weeks, however, indicating that telaprevir-resistant HCV remained sensitive to standard therapy. None of the eight patients who received telaprevir in combination with pegylated interferon experienced virological breakthrough during the 14-day study, including two with resistant virus.

Telaprevir has demonstrated a good safety profile so far, with no serious drug-related adverse events in the short term. It is currently in Phase IIb trials (PROVE 1 in the U.S. and PROVE 2 in Europe).

VALOPICITABINE

Douglas Dieterich (abstract 93) presented the latest data on valopicitabine (NM283), an oral HCV NS5B polymerase inhibitor being developed by Idenix Pharmaceuticals. As previously reported, valopicitabine in combination with pegylated interferon induced rapid virological suppression at four weeks in a Phase Ib trial that included 173 genotype 1 treatment-naïve participants receiving oral doses ranging from 200 to 800 mg/day; however, the drug caused significant gastrointestinal side effects at higher doses. As a result the clinical trial protocol was revised.

While rapid virological response rates were greater among patients receiving higher valopicitabine doses, follow-up data presented at AASLD showed that response rates in the different dose groups converged as treatment continued. By Week 12, 82%-92% of patients in the various arms experienced early virological response (≥ 2 log decline in HCV RNA). By Week 24, the percentages with undetectable HCV RNA were similar across the dose arms; 68% of subjects receiving valopicitabine 200 mg/day achieved HCV RNA below 20 IU/mL, compared with 67% in the 800 mg/day group. “At doses as low as 200 mg/day, valopicitabine plus pegylated interferon markedly suppresses viremia in treatment-naïve patients with HCV [genotype 1] infection,” the researchers concluded. The 200 mg/day dose was generally well-tolerated, with fewer adverse events than observed at higher doses. The study protocol was amended to

reduce the dose to 200 or 400 mg/day, and the 800 mg dose was discontinued.

OTHER ANTIVIRALS IN CLINICAL TRIALS

There were only a couple of presentations at AASLD on two other anti-HCV agents in development, Roche’s polymerase inhibitor R1626 (a prodrug of the nucleoside analog R1479) and the non-nucleoside NS5B polymerase inhibitor HCV-796, co-developed by ViroPharma and Wyeth Pharmaceuticals.

As reported by Stuart Roberts (abstract LB2), 47 genotype 1 patients in a Phase I trial were randomly assigned to receive either oral R1626 twice daily at one of four doses (500, 1500, 3000, or 4500 mg twice daily) or else placebo for 14 days. Final results were presented for patients who received the two higher doses. After 14 days, subjects taking R1626 experienced mean HCV RNA reductions of 2.6 and 3.7 logs, respectively, in the 3000 mg and 4500 mg dose arms. Dr. Roberts characterized the decline as “the best that we have seen with all the polymerase inhibitors studied so far.” R1626 exhibited good tolerability up to 3000 mg twice daily, although adverse events – including mild to moderate hematological changes – were observed at higher doses.

In a separate presentation (abstract 928), researchers reported that an *in vitro* analysis using an HCV replicon system demonstrated that R1479 (the active form of R1626 in the body) had moderate synergistic effects when combined with

continued on page 4

HealthWise:

Your Rights as a Patient



Lucinda K. Porter, RN

In October, the Los Angeles police department videotaped ambulance companies leaving ill patients in Skid Row. A representative from the ambulance company reported that hospital officials ask them to do this on a regular basis. Many of these dumped patients were homeless. A local council member spotted an obviously sick patient, dressed in a hospital gown, pushing a walker down the streets.

This is just plain wrong. The violation of patients' rights is a sad and indefensible reality. When we are sick, we are vulnerable. It is a basic human need to expect others to care for us when we are ill. However, these are expectations that are not always met. Sometimes the people we trust our health with *do not* live up to this trust.

The majority of my colleagues are kind, caring and dedicated. They work far more hours than they are supposed to, skip meals, and take their work home. Much of this is due to an overburdened health care system. Hospitals are understaffed and health care workers are overworked. When under stress, human beings cut corners. The amount and quality of time spent with patients may be compromised. While thinking about the trauma case in the next room, we may not listen as attentively. We might not act as compassionately as we feel. Our actions may not mirror our intentions. We may make mistakes.

But this does not justify unethical behavior. Patients always have the right to be treated humanely. However, I think it is important to understand the reality of modern health care. As patients, perhaps we can adapt to it without sacrificing good medicine.

The keys to navigating the health care system seem

to be persistence, good communication and self-advocacy. As in life, the "squeaky wheel" does get the grease. If you need something from your medical provider's office, such as a test result, keep calling until you get the result. Do not drop the ball. However, do this in a friendly, polite manner. A polite squeaky wheel makes more friends than someone who is rude. Friends are good to have when you need help.

How should you expect to be treated by your medical provider? What are your rights? There is not a simple answer to this question. In 1997, President Clinton appointed a commission to develop a plan to protect medical consumers. Since 2001, there have been a number of bipartisan attempts to pass legislation that would provide greater protection for patients. No federal Patients' Bill of Rights has passed the legislative and executive process.

Patients do have some protection. Nurses, physicians, and surgeons have codes of ethics to follow. Patients have very clear rights when using hospitals and skilled nursing facilities. Some states, such as California and New York, have basic Patients' Rights Bills. Various professional organizations prescribe patients' rights, such as the American Psychiatric Association and the Joint Commission on Accreditation of Healthcare Organizations.

Before any surgical procedure, you should be informed about the risks prior to consenting to the procedure. This is known as *informed consent*. All the risks should be listed, even if they are unlikely to occur. It may be frightening to read this information, so ask the doctor or nurse to be specific about the risk. For instance, it is scary to read that one of the risks of liver biopsy is death. However, when told that this occurs in 3 out of 10,000 procedures,

continued on page 7

AASLD: ANTIVIRALS

continued from page 2

either conventional interferon or ribavirin, with no increase in cellular toxicity. Combining R1479 with other anti-HCV agents produced additive effects. Based on results to date, Roche has started a Phase II trial of R1626 in combination with pegylated interferon plus ribavirin.

With regard to HCV-796, Stephen Villano and colleagues (abstract 1127) reported on a study in which 102 treatment-naive participants (72 with genotype 1) received the oral drug at various doses (50, 100, 250, 500, 1000, or 1500 mg) twice daily as monotherapy for 14 days. The maximum mean HCV RNA reductions from baseline were 1.4-1.5 log in the highest dose groups at Day 4. HCV NS5B gene sequence data, available for 58 genotype 1a patients, showed that viral load increases during HCV-796 monotherapy were associated with selection of viral variants with resistance mutations, including C316Y.

No new data were presented on Schering-Plough's protease inhibitor SCH 503034, which is currently being tested in prior pegylated interferon/ribavirin nonresponders in a large Phase II study following promising early results. It is important to remember that many investigational agents never make it out of the development pipeline, either due to suboptimal efficacy or poor safety, as illustrated by the Boehringer-Ingelheim protease inhibitor candidate BILN 2061, which was discontinued

due to cardiac toxicity in animal studies.

PRECLINICAL DATA

There were also several reports at AASLD on candidate anti-HCV agents that have yet to enter clinical trials. Hua Tan and colleagues (abstract 933) presented a poster on the oral HCV NS3/4A protease inhibitor ITMN-191, being developed by InterMune. In an *in vitro* study of ITMN-191 plus pegylated interferon using two HCV replicon systems, researchers found that the combination synergis-

“STAT-C drugs generally will be used in combination with pegylated interferon and possibly also ribavirin.”

tically inhibited HCV replication at low concentrations of both drugs, suggesting that co-administration could have a potential clinical benefit and provide a greater genetic barrier to the development of ITMN-191 resistance. Phase I trials are expected to begin soon.

Data were presented on several other antiviral agents further back in the development pipeline, including:

- **A-837093:** this NS5B polymerase inhibitor, being developed by Abbott Laboratories, suppressed HCV in genotype 1a and 1b replicon models and in chimpanzees; resistance emerged fairly rapidly when used as monotherapy, but synergistic activity and minimal cross-resistance were observed when combined with other

antiviral agents (abstracts 128, 417, 432).

- **ACH-806:** this Achillion Pharmaceuticals agent appears to work by blocking the HCV replicase complex, acting at a different stage of the replication process than protease inhibitors; viral variants resistant to ACH-806 and related compounds remained sensitive to other classes of anti-HCV agents (including NS3/4A protease and NS5B polymerase inhibitors) and vice versa (abstract 937).
- **AG-021541:** this Agouron/Pfizer non-nucleoside polymerase inhibitor exhibited anti-HCV activity *in vitro*, but viral variants with resistance mutations emerged, leading to reduced sensitivity to the drug (abstract 931).

IMMUNE-MODULATING THERAPIES

Researchers at AASLD also presented data on numerous experimental therapies that act at the level of the host immune system rather than against HCV itself, including:

- New forms of interferon, such as albumin interferon (Albuferon) and consensus interferon (Infergen);
- The toll-like receptor 9 agonist CPG10101 (Actilon), which activates dendritic cells, B-cells, and natural killer cells;
- The monoclonal antibody bavituximab;

continued on page 5

AASLD: ANTIVIRALS

continued from page 4

- Cyclophilin inhibitors, including SCY-635 and DEBIO-025;
- GI-5005, a yeast-derived targeted molecular immunogen, or “tarmogen.”

PROSPECTS FOR THE FUTURE

Experts at the satellite symposium discussed the implications of the novel targeted antiviral agents and how they might alter hepatitis C therapy. According to Dr. Jacobson, STAT-C offers the prospect of developing “regimens which can cure a substantially higher proportion of patients than is presently possible.”

Jean-Michel Pawlotsky said that there is “absolutely no doubt” that combination therapy is the wave of the future. While tomorrow’s treatment for hepatitis C may ultimately rely on oral “cocktails,” all agreed that for the foreseeable future, STAT-C drugs generally will be used in combination with pegylated interferon and possibly also ribavirin. However, the addition of antiviral agents may shorten the duration of therapy, thereby reducing the toxicity of pegylated interferon and ribavirin.

Further, use of antiviral agents in conjunction with immune-based therapies holds promise especially for “difficult to treat” patients such as prior nonresponders and relapsers. Dr. Jacobson noted that it is not yet clear what happens when HCV is suppressed. The virus may remain present at very low levels in “reservoir” sites

outside the liver, which could lead to relapse after completion of therapy. The answer to this mystery may determine whether immune modulators will always be needed in addition to antiviral agents.

The speakers also shared concerns about resistance to the antiviral agents. According to Dr. Pawlotsky, resistance cannot be avoided, but “it can be delayed or managed.” Charles Rice suggested that we can expect that therapy for hepatitis C will become more complicated, like highly active antiretroviral therapy (HAART) for HIV, which revolutionized treatment but presents clinicians and patients with a “bewildering” array of therapeutic options.

All STAT-C agents now in development can select for resistance if used as monotherapy. The emergence of resistance mutations can be delayed by simultaneous use of multiple agents that attack HCV at different stages of its lifecycle. Suppressing viral replication to the greatest possible extent is the best way to prevent resistance, and therefore good adherence to therapy is critical. “As with HIV, we have to become more sophisticated about resistance,” Dr. Jacobson cautioned.

In conclusion, John McHutchison said that despite their uncertainties and potential drawbacks, the development of antiviral agents that directly target HCV is a “very exciting” treatment advance. Added Dr. Jacobson, “STAT-C is a leap forward of the magnitude of HAART.”



EXCITING NEW PUBLICATIONS FROM HCSP

HEPATITIS C

HCSP GUIDES

- *A Guide to Understanding Hepatitis C 2006*
- *For Family and Friends: Caring for Someone with Hepatitis C*

MEDICAL WRITERS' CIRCLE

- *HIV-HCV Coinfection Update*

HCSP FACTSHEETS

Hepatitis C Basics:

- *Fatty Liver*
- *What Is Fibrosis/Cirrhosis?*
- *New HCV Antivirals and Drug Resistance*

HCSP Factsheet Series

- *HCV Viral Load Tests*
- *Predictors of HCV Treatment Response*

HEPATITIS B

- *Hepatitis B: What You Need to Know*
- *What Are Antivirals?*
- *HBV: Drugs in Current Clinical Development*
- *What's New in Hepatitis B Treatment*

ALASKA DONOR REGISTRY

This fall, the Census Bureau estimated that the United States population passed the 300 million mark. A very small percentage of this figure lives in our largest state, Alaska. With a population of a little more than 600,000, Alaska claims fewer residents than San Francisco. One amazing statistic about Alaskans is that 43% of the population is registered as organ donors. Thank you Alaska – you are an inspiration.

For the rest of you Alaskans, if you want to register as a potential organ donor, you may indicate you wish on your state driver’s license or identification card. Remember to notify your family about this. You may register or verify your registration electronically at <http://alaskadonorregistry.com>

**Help Us Reach More People with Hepatitis C!
SUPPORT US THROUGH EITHER A PAID SUBSCRIPTION OR DONATION**

YES! I'd like to subscribe

\$20 one year—12 issues

\$10 one year—12 issues
(for those with fixed incomes)

Renewal

NAME _____

ADDRESS _____

CITY _____

STATE _____ ZIP _____

**YES! I'd like to make
a tax deductible donation**

\$10 \$25
 \$100 other

Please make checks payable to: HCSP/The Tides Center

Please mail form to:

HCV ADVOCATE
P.O. Box 427037
San Francisco, CA 94142-7037



The Hepatitis C Support Project does not share its mailing list with any individual or organization. All subscribers' names and addresses are strictly confidential

RIGHTS

continued from page 3

this risk does not seem as frightening. If you are healthy, had the necessary lab work, and have an experienced physician, this risk is even less.

Patients have clear rights regarding the handling of healthcare information. Under the Health Insurance Portability and Accountability Act (HIPAA), you have the right to privacy and access to your medical information. You have the right to be notified when your information is being shared, with whom it is being shared, and, in certain cases, the power to decide if the information may be shared. You have the right to make corrections to your medical information and to file complaints if any of these rights are violated.

If you participate in any clinical research, your rights are highly protected. Before a clinical trial can begin, it must meet the strict set of standards required by the U.S. Food and Drug Administration (FDA). Additionally, an independent review board must approve every trial before human subjects can be enrolled. This board is composed of people from many disciplines – doctors, scientists, pharmacists, nurses, and non-scientist community representatives such as attorneys, clergy or lay people. Clinical trials are reviewed throughout the course of the study, and all people associated with the trial are required to keep records long after the study has ended. Participants must be informed of their rights, including the right to drop out of a study for any reason

without influencing their subsequent medical care.

A few days after the story about patient dumping, the news media reported another story about hospitals. This story represented the best side of medicine. In an effort to reduce emergency room visits, some hospitals are offering free basic medical care on an outpatient basis. Their goal is to deal with medical issues before they become crises. This is a compassionate approach and one that I hope is practiced everywhere. More importantly, it is refreshing to hear some good news about health care.

FOR MORE INFORMATION:

- **HIPAA** www.hhs.gov/ocr/hipaa
1-866-627-7748
- **Americans with Disabilities Act, Social Security or the Family Medical Leave Act:**
A Guide to Hepatitis and Disabilities (under HCSP Guides) and *HCV Benefits and Disability Issues* (in the Fact Sheet section) www.hcvadvocate.org
- **The rights of clinical trial participants:**
A Guide to Understanding Clinical Trials and Medical Research in Hepatitis C (under HCSP Guides) www.hcvadvocate.org



Executive Director Editor-in-Chief, HCSP Publications

Alan Franciscus
alanfranciscus@hcvadvocate.org

Managing Editor, Webmaster

C.D. Mazoff, PhD
cdmazoff@hcvadvocate.org

Contributing Authors

Liz Highleyman
Lucinda K. Porter, RN

Design

Paula Fener
Blue Kangaroo Design
blueroodesign@aol.com

Contact information:

Hepatitis C Support Project
PO Box 427037
San Francisco, CA 94142-7037

The HCV Advocate offers information about various forms of intervention in order to serve our community. By providing information about any form of medication, treatment, therapy or diet we are neither promoting nor recommending use, but simply offering information in the belief that the best decision is an educated one.

Reprint permission is granted and encouraged with credit to the Hepatitis C Support Project.

© 2006
Hepatitis C Support Project

For Living Positively. Being Well.



www.hcvadvocate.org

HCSP

P.O. Box 427037
San Francisco, CA
94142-7037