

HCV ADVOCATE WEEKLY NEWS REVIEW

Review of HCV, HBV and HIV/HCV Coinfection Related News and Highlights

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Editor-in-Chief*

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Aug 31, 2008

***New Approach, Old Drug Show Promise Against Hepatitis C,
Research Shows***

<http://www.sciencedaily.com>

ScienceDaily (Sep. 2, 2008) — The fight against the liver disease hepatitis C has been at something of an impasse for years, with more than 150 million people currently infected, and traditional antiviral treatments causing nasty side effects and often falling short of a cure.

Using a novel technique, medical and engineering researchers at Stanford University have discovered a vulnerable step in the virus' reproduction process that in lab testing could be effectively targeted with an obsolete antihistamine.

The advance involves two new discoveries. One is that a protein called NS4B is instrumental in binding some of the genetic material, or RNA, and allowing the hepatitis C virus to replicate. The other is that the *former anti-itching drug clemizole hydrochloride* could hinder that protein, resulting in a tenfold decrease in virus replication with no apparent harm to infected liver-like cells. Because the drug has already been used by people, it is eligible for human testing.

"We're excited about this and we're actively moving forward toward clinical trials," said virology expert Jeffrey Glenn, MD, PhD, associate professor of gastroenterology and hepatology. Glenn is one of two senior authors of the paper. The lead authors are postdoctoral scholars Shirit Einav, MD, in medicine, and Doron Gerber, PhD, in bioengineering.

One of the team's key discoveries used coin-sized microfluidic chips that shrink tabletop biological experiments down to the tiny scale of nanoliters. The paper marks the first time that microfluidic technology has been used to discover a specific drug, said Stephen Quake, PhD, professor of bioengineering and the other senior author of the paper. In fact, the small team was able to screen more than 1,200 drug candidates and find clemizole in just two weeks, Gerber added.

"That's just an example of the power of these microfluidics automation technologies that one or two people working together can actually screen very large numbers of compounds," Quake said. "Big pharmaceutical companies have very large teams and a lot of infrastructure. We're trying to reinvent the whole process."

As director of Stanford's Center for Hepatitis and Liver Tissue Engineering, Glenn focuses his research on trying to expand the number of drug targets for the disease. After using molecular virology techniques to study the NS4B protein, he and Einav began to suspect it could be such a target.

However, like other proteins associated with cellular membranes, NS4B is difficult to purify in large quantities while retaining the protein's natural properties and functionality.

But the advantage of microfluidics, Quake said, is that the volumes needed for a successful experiment are quite small, meaning that researchers can get by with very little purified, properly functioning protein. What is insufficient for a benchtop experiment is plenty in microfluidics.

"It lets us redefine the notion of success," Quake said.

Ultimately the researchers discovered that NS4B is an essential player in the virus' process of binding RNA. This is a necessary step in the virus' replication process and, through careful

observation, the team determined where it binds and how strongly. That led them to realize which kind of drug - a small-molecule compound - could block that interaction.

Even then, however, the team had to solve another problem, which is the propensity for small-molecule drugs, such as clemizole, to get absorbed into the silicone of the chip itself. Gerber said he worked around that by printing the drug onto the chip directly where the interaction with NS4B would occur. That meant the drug didn't have to move through the chip's plumbing and enough would interact with the protein.

In all, the team found 18 drugs that substantially reduced NS4B binding to its target RNA, but they focused on clemizole because it is already known to be safe in humans. Quake said several of the other compounds were also interesting starting points for developing useful medicines.

Should clemizole prove effective in human trials, Glenn said, it could become an essential component in a new class of multidrug treatments for hepatitis C. Other components could be drugs under development elsewhere that target specific enzymes in the virus. The goal is to improve on the current treatment, a combination of the general antiviral drugs interferon and ribavirin. Those only work about half the time, but have uncomfortable, flulike side effects.

"[Clemizole] does have the potential to be part of a cure, because the idea is not to use it on its own but as a cocktail component," Glenn said.

Similarly it took a cocktail of research expertise to come up with this new assault on the hepatitis C virus, Quake said.

"Neither Jeff's group nor mine could have done this on our own," Quake said. "It was enabled by both of us bringing our pieces to the table: the questions he was asking and the technology we developed."

The new research will be published in the Aug. 31 online version of *Nature Biotechnology*.

The other authors of the paper are doctoral student Paul Bryson; postdoctoral scholar Ella Sklan, PhD; research associate Menashe Elazar, PhD, and Sebastian Maerkl, PhD, a former member of Quake's group and now an assistant professor at the Ecole Polytechnique Federale de Lausanne in Switzerland.

The research was funded by a Burroughs Wellcome Fund Clinical Scientist Award in Translational Research, the National Institutes of Health, the Fulbright Foundation and an American Liver Foundation Postdoctoral Fellowship Award.

Sep 1, 2008

Mobile health units come to Ferndale this fall

<http://www.hometownlife.com>

-By Megan Pennefather

While Ferndale volunteers try to get the city's first free clinic up and running by the end of this year, free health care will be available this fall in the form of mobile health units.

On the first Thursday of the month from September through December, free mobile health clinics will set up shop around the city, offering blood pressure checks, blood sugar checks, cholesterol checks, weight screening, HIV screening and counseling, Hepatitis C screening and counseling and other preventive health checks or screenings.

The mobile units, which are free and open to residents and non-residents alike, are sponsored by the Detroit Department of Health and Wellness, which received a grant to provide the service in the city and its surrounding suburbs.

Ann Heler is chairperson of the FernCare Free Clinic advisory board, a volunteer group charged with raising money to start a free clinic in Ferndale. FernCare is co-sponsoring the mobile health units in order to drum up visibility for the clinic.

"We wanted to associate health care and health issues with FernCare, and we thought this would be a good way to do that," she said.

As to the status of the free clinic, it's still scheduled to open either at the end of this year or in January. The FernCare volunteer group recently applied for 501(c)3 nonprofit status.

The group has found two possible locations, though Heler won't say where until one is chosen. After that, she said, an architect will be found to renovate a building into a full-service clinic.

Then, she added, "it's just a question of getting the wonderful people who've volunteered together and figure out times" the clinic will be open.

Meanwhile, the mobile health units will be available Sept. 4, Oct. 2, Nov. 6 and Dec. 4. From 10 a.m. to 2 p.m. the clinic will be located in the Oakland Livingston Human Services Agency parking lot, 344 E. Nine Mile, across the street from Credit Union One. From 3-6 p.m., the health unit will be at Ferndale Foods on West Nine Mile at Livernois.

For more information on FernCare, visit www.ferncare.org .

-By Megan Pennefather

Cancer patient in NHS drug funding row

<http://www.telegraph.co.uk>

by Graham Tibbetts

A cancer sufferer whose disease was linked to an NHS blood transfusion has been told the health service will not pay for his treatment.

Timothy Nolan, a father of four, has had to pay out £2,700 a month for the drug Nexavar to prolong his life.

The former construction manager was diagnosed with liver cancer three years ago as a result of contracting Hepatitis C from infected blood following an accident in 1985.

In 2006 it was disclosed that the NHS bought batches of blood contaminated with HIV and Hepatitis from sources including American prisons.

However, Mr Nolan, 68, has twice been turned down for funding for Nexavar by East Birmingham Health Trust.

"They found the Hepatitis C was from the transfusions in 1985," he said.

"Six months later they discovered a tumour in my liver, a primary cancer caused by the disease.

"My consultants recommended Nexavar last October. I applied for funding but I was turned down. I have been using my savings to pay for the drug. It has reduced the tumour."

Mr Nolan, who has 13 grandchildren, added that the NHS should have warned the blood transfusion patients that they were at risk of infection.

A spokesman for the health trust said: "Sorafenib, also known as Nexavar, is not currently licensed for the treatment of liver cancer.

"As a result, the Trust does not routinely fund its use for patients."

More than 1,000 people have died so far following contaminated blood transfusions, with thousands more terminally ill. An inquiry into the matter is due to conclude later this year.

In January the Ministry of Defence said gravely wounded British soldiers may have received contaminated blood from America. Around 18 personnel were at risk of infection, although the MoD stressed that the risk of infection was low.

Sep 2, 2008

Progenitor cells eyed for liver transplants

www.reuters.com

NEW YORK (Reuters Health) - German researchers report they have isolated progenitor cells, the stage above stem cells, from human liver specimens. When transplanted into mice, the cells show signs of "taking" and becoming new liver cells.

Dr. Thomas S. Weiss of the University of Regensburg Hospital and colleagues identified the progenitor cells by surface "markers," which indicated that they were capable of becoming liver cell or cells of the bile duct.

As reported in the medical journal *Gut*, the investigators demonstrated the potential ability of the cells to become these different types in lab dish experiments.

Transplantation of the cells into the livers of immune-suppressed mice resulted in "engraftment," and tests showed the cells functioned as they should.

Weiss' team concludes that it's possible to isolate liver progenitor cells, and that they "might be a potential candidate for cell treatment in liver diseases."

SOURCE: Gut, August 2008.

Walter Reed Evaluation Concludes OraQuick(R) HCV Test is Preferred Over Other Rapid Tests

<http://www.marketwatch.com>

- OraQuick(R) HCV Test Found to Have Higher Sensitivity and Specificity Than Other Rapid HCV Tests -

BETHLEHEM, Pa., Sep 02, 2008 (BUSINESS WIRE) -- OraSure Technologies, Inc. (OSUR 5.09, -0.04, -0.8%) , a market leader in oral fluid diagnostics, today announced that an evaluation by the Walter Reed Army Institute of Research of the OraQuick(R) HCV Test, currently in clinical development by OraSure Technologies, was recently released at the Advanced Technology Applications for Combat Casualty Care meeting, sponsored by the Department of Defense. The purpose of the evaluation, entitled "Laboratory Evaluation of Hepatitis C Rapid Test for Use in Screening Walking Blood Bank Donors," was to determine the best rapid HCV test to use for screening blood donors for hepatitis C ("HCV") in the theater of war. The OraQuick(R) HCV test was selected as the preferred test based on all facets of the evaluation.

Blood that is donated to commercial or hospital blood banks is subjected to extensive testing for blood-borne pathogens before it is released to be used in transfusions. However, emergency battlefield conditions sometimes dictate that an available soldier, or Walking Blood Bank, donate without this normal lab-based testing being available. A rapid assay such as the OraQuick(R) HCV test can add a measure of safety against this important blood borne virus.

Five rapid tests were initially selected from the rapid HCV tests available worldwide, based on an evaluation of published claims and sensitivity testing using HCV positive samples. The tests were then compared in a comprehensive evaluation of test performance using plasma and blood specimens. The study indicated that the OraQuick(R) HCV test had the highest sensitivity (99.4%) and the highest specificity (99.7%) among the tests evaluated. In addition, the evaluation indicated that the OraQuick(R) HCV test detected HCV antibodies approximately three days sooner than available laboratory-based enzyme immunoassays and approximately sixteen days earlier than the next most sensitive rapid HCV test. Early detection of seroconversion is an important measure of the sensitivity of a test and means that hepatitis C infection can be identified even with relatively recent exposure.

"We are very pleased with the results of the Walter Reed evaluation," said Stephen R. Lee, Ph.D., Chief Science Officer of OraSure Technologies. "We are eager to complete our clinical trials for the OraQuick(R) HCV test and submit our applications for both FDA approval and CE registration for this product. Based on the performance data generated to date, we believe this test will play an important future role in identifying new HCV infections and enabling infected individuals to receive the care and treatment they need."

The study was conducted at The Walter Reed Army Institute of Research and involved investigators from the Walter Reed Army Institute of Research Division of Retrovirology, The U.S. Military HIV Research Program, Walter Reed Army Institute of Research Division of Military Casualty Research, the U.S. Army Blood Program, the Army Medical Department Center and School, the Robertson Blood Center and the American Red Cross. Conference information may be obtained at [https:// www.usacc.org/ATACCC/index.htm](https://www.usacc.org/ATACCC/index.htm)

The OraQuick(R) HCV rapid test is not currently approved by the U.S. Food and Drug Administration ("FDA") for use or sale in the United States. OraSure Technologies is currently conducting clinical trials to obtain FDA approval for the test utilizing multiple specimen types including oral fluid, finger-stick and venous whole blood, plasma and serum. The clinical studies are nearing completion and a pre-market application is expected to be submitted to the FDA in the near future. An application for CE mark approval, which is required to sell the test in the European Union, is expected to be filed shortly after the FDA submission.

Approximately 170 million people are chronically infected with hepatitis C worldwide, and there are approximately three to four million new HCV infections each year on a global basis. Chronic hepatitis C can cause cirrhosis, liver failure and liver cancer. About half of all cases of primary liver cancer in the developed world are caused by hepatitis C, and hepatitis C-related liver disease is now the leading cause for liver transplants. Most people who develop chronic hepatitis C infection are not aware that they have the disease. Identification and treatment of occult infections could significantly reduce future morbidity and mortality associated with HCV infection.

About OraSure Technologies

OraSure Technologies develops, manufactures and markets oral fluid specimen collection devices using proprietary oral fluid technologies, diagnostic products including immunoassays and other in vitro diagnostic tests, and other medical devices. These products are sold in the United States as well as internationally to various clinical laboratories, hospitals, clinics, community-based organizations and other public health organizations, distributors, government agencies, physicians' offices, and commercial and industrial entities.

OraSure Technologies is the leading supplier of oral-fluid collection devices and assays to the life insurance industry and public health markets for the detection of antibodies to HIV. In addition, the Company supplies oral-fluid testing solutions for drugs of abuse testing. For more information on the Company, please go to www.orasure.com.

About the Walter Reed Army Institute of Research

Walter Reed Army Institute of Research (WRAIR) is the largest, most diverse, and oldest laboratory in the US Army Medical Research and Materiel Command. It conducts research on a range of militarily relevant issues, including naturally occurring infectious diseases, combat casualty care, operational health hazards, and medical defense against biological and chemical weapons. WRAIR is the Department of Defense's lead agency for infectious disease research and a crucial source of research support for medical product development.

About the United States Military HIV Research Program

The U.S. Military HIV Research Program (USMHRP) is dedicated to HIV vaccine development, prevention, disease surveillance and care and treatment for HIV. This program builds on the

strength of the U.S. military medical research community, and addresses specific HIV research requirements to meet its mission: prevention of HIV-1 disease in the active force and, by extension, the global community at risk of infection. USMHRP's extensive diagnostics expertise including familiarity with HIV rapid tests led the U.S. Army Blood Program to engage with USMHRP for this HCV rapid test evaluation. USMHRP information may be found at <http://www.hivresearch.org/index.html>

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Long Waiting Lists for Organ Transplants in Iceland

<http://www.icelandreview.com>

Physicians at the national hospital of Iceland, Landspítali – University Hospital, have requested that the Ministry of Health reconsider an agreement on organ transplants with the national hospital of Denmark because of long waiting lists.

Patients in Iceland sometimes have to wait up to two years for a new liver and even longer for kidneys. “The waiting period in Denmark is too long,” senior physician in Landspítali’s kidney division Runólfur Pálsson told Morgunbladid. “The need is increasing among us and therefore we are worried.”

Sigurður Ólafsson, gastroenterologist and hepatologist at Landspítali, said it is timely to examine whether agreements on organ transplants can be reached with hospitals other than the national hospital of Denmark.

Every year one to three Icelanders have a new liver transplanted at The Kingdom’s Hospital in Copenhagen where about the same amount of Icelanders get new kidneys per year. In both Norway and Sweden the waiting lists are much shorter, only about six weeks.

The reason for this development is that liver diseases are increasing in Denmark and at the same time the supply of organs is low, lower than in the other Nordic countries. Since 1993, Icelanders have donated organs to a joint Nordic organ bank and in that period received fewer organs than they have donated.

Liver diseases are on the rise in many parts of the world, primarily because of higher alcohol consumption, drug use and obesity. Cirrhosis is still less common in Iceland than neighboring countries, but that seems to be about to change.

“We are no different from other Western nations, we are only a few years behind,” Ólafsson said.

Cases of hepatitis C and B are on the rise in Iceland, increasing considerably last year. Last year there were 95 cases of hepatitis C in Iceland compared to 56 in 2006. At the same time cases of hepatitis B increased from 16 to 48.

Alcoholism is by far the most common cause of cirrhosis (in 50 to 70 percent of all cases) and hepatitis C is the second most common cause (eight to 12 percent).

InterMune Earns Development Milestone in HCV Protease Inhibitor Collaboration With Roche

<http://www.earthtimes.org>

- \$15 million development milestone payment to InterMune - - Roche to lead ITMN-191 program in Phase 2 -

BRISBANE, Calif., Sept. 2 /PRNewswire-FirstCall/ -- InterMune, Inc. (Nasdaq: ITMN) today announced that InterMune has earned a \$15 million development milestone under its development collaboration with Roche for the hepatitis C virus (HCV) NS3 protease inhibitor compound **ITMN-191** (referred to as **R7227** at Roche), currently in a Phase 1b clinical trial in combination with Pegasys(R) (peginterferon alfa-2a) and Copegus(R) (ribavirin).

Under the terms of their 2006 collaboration agreement, the clinical program for ITMN-191 is now being transitioned to Roche which, starting in Phase 2, will have primary responsibility for completing the global development and registration program.

Nick Cammack, Ph.D., Global Head of the Virology Disease Biology Area, Roche, said, "Protease inhibition is a crucial aspect of our HCV strategy, which is focused on developing clinically differentiated medicines for patients. Our continued enthusiasm for ITMN-191/R7227 underscores our confidence in InterMune and we now plan to rapidly move the program into Phase 2 development."

Dan Welch, Chairman, Chief Executive Officer and President of InterMune, said, "We are very pleased to have led the preclinical development, conducted three Phase 1 clinical trials and with Roche, optimized the manufacturing of ITMN-191 active pharmaceutical ingredient (API) since the collaboration was announced less than two years ago. We look forward to the continued strong relationship with Roche as we together develop protease inhibitor therapies in combination with current standard of care and with other direct antiviral agents."

About the Roche/InterMune Collaboration

In October 2006, Roche and InterMune announced an exclusive worldwide collaboration to develop and commercialize products from InterMune's HCV protease inhibitor program, including ITMN-191. The companies also collaborate on a research program to identify, develop and commercialize novel second-generation HCV protease inhibitors.

At closing, InterMune received from Roche an upfront payment of \$60 million, and in 2007 received a \$10 million manufacturing milestone and a \$10 million development milestone. In addition to the \$15 million milestone being announced today, assuming the continued successful

development and commercialization of ITMN-191 in the United States and other countries, InterMune could potentially receive up to an additional \$435 million in milestones.

Roche funds 67% of the global development costs of ITMN-191. The companies will co-commercialize the product in the United States and share profits on a 50/50 basis. InterMune will receive royalties outside the United States.

Roche has rights to other HCV protease inhibitor development candidates resulting from the research collaboration. The economic terms for ITMN-191 also apply to additional compounds that InterMune and Roche may develop and commercialize.

In early April 2008, InterMune reported top-line results in the four dose cohorts of treatment-naive patients in a Phase 1b multiple-ascending-dose (MAD) monotherapy trial of ITMN-191 in patients chronically infected with HCV genotype 1. ITMN-191 demonstrated significant and rapid viral kinetic activity and excellent safety and tolerability in all dosage regimens. Also in early April, InterMune announced that 13-week preclinical studies in rats and monkeys were successfully completed which were necessary before initiation of clinical studies in Phase 2 with longer treatment durations than those performed to date with ITMN-191.

In late May 2008, InterMune initiated a 14-day study of ITMN-191 in combination with Pegasys(R) (peginterferon alfa-2a) and Copegus(R) (ribavirin). The study is proceeding as planned. Top-line results from the triple combination study are anticipated to be released in the fourth quarter of 2008.

SOURCE InterMune, Inc.

Morticians plead guilty to body snatching

<http://politicom.moldova.org>

Two Philadelphia morticians have pleaded guilty to being part of a body-snatching ring that illegally harvested parts for surgical usage.

Louis Garzone, 65, and his brother, Gerald, 48, allegedly collected \$1,000 a corpse for letting a North Jersey tissue bank dismember 244 bodies, some infected with HIV or hepatitis, without permission from relatives, *The Philadelphia Inquirer* reported. They could be sentenced to life in prison. Sentencing was set for Oct. 22, the report said.

The Garzones' pleas came as jury selection in their trial was set to begin. Three others have pleaded guilty in the scheme and were reportedly prepared to testify against them.

They included the founder of Biomedical Tissue Services, Michael Mastromarino, 44, a former oral surgeon who is serving an 18- to 54-year prison term in New York resulting from similar convictions. He allegedly earned \$4 million harvesting and selling parts from 1,077 bodies obtained from funeral homes in New York, New Jersey and Pennsylvania.

Also agreeing to testify against the Garzones were James J. McCafferty, their partner in a Philadelphia crematorium, and the chief cutter from Mastromarino's tissue harvesting operation, the *Inquirer* said.

Sep 3, 2008

Recommendations for Adefovir Dipivoxil (Hepsera) Usage May Reduce Risk for Resistance

www.medscape.com

On May 27, the FDA approved safety labeling revisions for adefovir dipivoxil (Hepsera; Gilead Sciences, Inc) to advise of the potential for clinical resistance.

Resistance to adefovir can result in viral load rebound and exacerbation of hepatitis B virus infection (HBV), potentially leading to liver decompensation and fatal outcome in patients with diminished hepatic function.

To decrease the risk for resistance in patients with lamivudine-resistant HBV, adefovir should be administered in combination with lamivudine rather than as monotherapy. For those receiving adefovir alone, treatment modifications should be considered if serum HBV DNA levels remain above 1000 copies/mL with continued therapy.

The latter recommendation is based on long-term (144-week) data from an adefovir clinical trial (n = 124), in which HBV DNA levels greater than 1000 copies/mL at week 48 were associated with an increased risk for the development of resistance.

Adefovir is indicated for the treatment of HBV in patients aged 12 years and older who have evidence of active viral replication and either persistent elevations in serum aminotransferases or histologically active disease.

Intercell AG Announces Favourable Six Months Follow-Up Results from HCV Vaccine

<http://www.medadnews.com>

- *Long term follow up results from chronically infected Hepatitis C patients strongly confirm and exceed positive data obtained earlier in 2008*
- *Study is the first to show a statistically significant and long-term antiviral effect of therapeutic Hepatitis C vaccination*
- *Data pave the way and strongly support move into a second generation vaccine formulated with Intercell's adjuvant IC31® acting through TLR activation*

Vienna, Austria, September 3, 2008 – Today, Intercell AG (ICLL) announced the six months follow up data of its exploratory clinical Phase II study targeting treatment-naïve Hepatitis C genotype-1 patients. As previously reported in February 2008, in this trial the therapeutic Hepatitis C vaccine (IC41) comprising five synthetic T-cell peptides and Intercell's first-generation poly-Arginine adjuvant (IC30) disclosed a statistically significant reduction of

viral load in the blood of chronically infected patients up to 2 weeks after the last vaccination. The current long term follow up results show that this reduction was significantly more pronounced at six months after the final vaccination.

In the open label controlled multicenter Phase II study 50 genotype-1 patients, naïve to standard treatment were enrolled for receiving a treatment schedule consisting of 8 intradermal IC41 vaccinations in biweekly intervals with topical application of the Toll-like receptor (TLR) agonist imiquimod. The previous analysis of 46 patients at 2 weeks after the last vaccination with IC41 showed already a statistically significant ($p=0.001$) HCV RNA decline of 0.2 log. The present follow-up data from 33 patients at six months after end of IC41 vaccination revealed an even greater viral load decline of 0.46 log ($p=0.001$). Interestingly, the virus decline (0.6 log) at the six months time point was most pronounced in patients with high initial viral load (> 2 million copies/ml). A parallel study arm conducted in 21 treatment-naïve patients where the imiquimod application was omitted, did not show a significant reduction of the viral load. Thus the results strongly support the notion that the future coadministration of a TLR adjuvant, like IC31®, is pivotal for the therapeutic effect of the vaccine.

"Our study is the first report to show significant long-term viral load effects of therapeutic vaccination. In particular the increasing RNA decline up to 6 months after vaccination is extremely encouraging and finally suggests the formulation of our vaccine with IC31®, a strong TLR agonist. Furthermore our vaccine in future trials may be combined with standard therapy or novel antivirals." states Alexander von Gabain, Chief Scientific Officer of Intercell. Although options for the treatment of chronic Hepatitis C with Interferon/Ribavirin have improved, treatment will remain very difficult and a significant unmet medical need, especially in the case of Genotype 1. Novel immunotherapies, and possibly therapeutic vaccines, might become an option in the arena of existing and future HCV combination treatments. Thus, Intercell will follow its development strategy that will also take advantage of an enlarged antigen portfolio and of IC31®, Intercell's second-generation adjuvant that has recently demonstrated the generation of T-cell responses, in human vaccine trials, to a level not yet seen for other known adjuvants.

About Intercell AG

Intercell AG is a growing biotechnology company that designs and develops novel vaccines for the prevention and treatment of infectious diseases with substantial unmet medical needs. The Company's technology platforms include an antigen-discovery system, two proprietary adjuvants and a novel patch-based delivery system. Based on these technologies, Intercell has strategic partnerships with a number of global pharmaceutical companies, including Novartis, Merck & Co., Inc., Wyeth, Sanofi Pasteur, Kirin and the Statens Serum Institut.

The Company's lead product is a vaccine against Japanese Encephalitis. That vaccine successfully concluded pivotal Phase III clinical trials in 2006, and Intercell is seeking marketing approval in the United States, Europe, Australia and Canada. Approval in those markets is anticipated during the second half of 2008.

The Company's development pipeline includes Phase II vaccine programs for *Pseudomonas* (in-house development) and *S. aureus*, which is being developed with Merck & Co. Inc. The Company's novel Travelers' Diarrhea vaccine patch will enter Phase III testing in 2009. Intercell is also in clinical trials of a vaccine enhancement patch with injected pandemic influenza

vaccines (one shot plus patch). In addition, five other products focused on infectious diseases are in preclinical development.

Intercell is listed on the Vienna stock exchange under the symbol "ICLL".

For more information, please visit: www.intercell.com

HBV Vaccine Nonresponders May Respond to Combined Hep A/B Vaccine

www.reuters.com

NEW YORK (Reuters Health) Sept 02 - For the 5% to 10% of adults who fail to mount an adequate response to the standard hepatitis B virus (HBV) vaccine regimen, a double dose of the combined hepatitis A and B vaccine may turn these nonresponders into responders, results of a study from Sweden suggest.

Most guidelines recommend a repeated course of the standard HBV vaccine in people who fail to develop protective levels of antibodies to hepatitis B surface antigen (anti-HBs).

Instead of repeating the standard HBV vaccine regimen in nonresponders, Dr. Kristina Cardell from University Hospital, Linköping and colleagues opted to administer the combined hepatitis A and B vaccine. Their study involved 48 healthcare workers who failed to respond to the HBV vaccine and 20 control subjects nave to the HBV vaccine.

After the first dose of the combined vaccine, protective levels of anti-HBs were achieved in 59% of HBV vaccine nonresponders and 10% of control subjects, the investigators report in the August 1 issue of the *Journal of Infectious Diseases*. After 3 doses, 95% of prior nonresponders and 100% of controls had developed a response.

"This is most likely explained by the increased dose, a positive bystander effect conferred by the hepatitis A vaccine, or both," Dr. Cardell and colleagues say.

In a commentary, Dr. Helmut M. Diepolder from University of Munich, Germany, writes, "These results are among the best achieved in comparable studies using revaccination with the standard hepatitis B vaccine and are comparable to results from revaccination studies using the pre-S1/S2 vaccine or vaccines with new adjuvants."

"Importantly, the combined vaccine was well tolerated and is, thus, an interesting option to use in hepatitis B nonresponders who are negative for antibodies to hepatitis A virus," Dr. Diepolder adds.

J Infect Dis 2008;198:297-304.

Sep 4, 2008

FDA Approves First Hepatitis B Viral Load Test

<http://www.marketwatch.com>

Another Roche first in TaqMan(R) real-time PCR testing for the diagnostic lab

PLEASANTON, Calif., Sept 04, 2008 /PRNewswire via COMTEX/ -- The U.S. Food & Drug Administration (FDA) has approved the Roche COBAS(R) TaqMan(R) HBV Test, the first assay for quantitating Hepatitis B Virus DNA approved in the U.S. The test uses Roche's real-time PCR technology to quantify the amount of Hepatitis B virus DNA in a patient's blood. Doctors may use viral load testing results to establish a baseline level of infection and during treatment as an aid in assessing individual responses to therapy. Widespread application of antiviral therapy along with the Hepatitis B vaccine has helped reduce prevalence; however, Hepatitis B remains a serious and potentially life threatening global disease, potentially resulting in death from extensive liver damage or liver cancer for chronically infected people.(1)

"Viral load testing with an FDA approved test has long been the standard for managing patients with HIV and Hepatitis C," said Teresa Wright, M.D., Chief Medical Officer at Roche Molecular Diagnostics. "Availability of this new Roche test enables doctors and laboratories to bring that same level of standardized viral load measurement to Hepatitis B treatment."

Because the goal of Hepatitis B therapy is to treat until the virus is undetectable in the patient's blood, it is critical for viral load monitoring tests to be able to quantify very low levels of virus. Similarly, it is important for the test to quantify very high levels of virus (higher than 100 million IU/mL), an indicator of the need for more or less aggressive treatment. The Roche COBAS(R) TaqMan(R) HBV Test can detect the World Health Organization (WHO) HBV International Standard in plasma and serum as low as 3.5 IU/mL and 3.4 IU/mL respectively. The test can measure HBV DNA as high as 1.10E8 IU/mL, representing a significantly broader dynamic range than previously available tests in the U.S.

Other infections concomitant with Hepatitis B are common, with up to 10% of HIV patients in the US also infected with Hepatitis B virus. This makes it essential for the test to quantitate the HBV virus in presence of other viruses.

Designed for use with the High Pure System, the test is run on the COBAS(R) TaqMan(R) 48 analyzer and gives labs the added benefits of automated real-time PCR. The test system benefits from the same contamination control protection designed into all COBAS(R) TaqMan(R) assays, including closed-tube processing and built-in Roche-proprietary AmpErase enzymes. To help with needed standardization, the Roche COBAS(R) TaqMan(R) HBV Test has been calibrated with the WHO standard and reports with the international unit of measure IU/mL. The test was designed to quantify all major Hepatitis B genotypes, including pre-core mutants that can lead to more severe liver disease and reduced response to antiviral therapy.

Roche Diagnostics, a leader in molecular diagnostics, has more than 10 years of global experience in HBV viral load testing and has actively monitored virus mutation through its Global Surveillance program. The COBAS(R) TaqMan(R) HBV Test is the latest in a portfolio of increasingly automated real-time PCR Hepatitis and HIV tests that Roche is developing. The company's fully automated, real-time HIV monitor test was approved by the FDA in May 2007

and the company has filed a Premarket Approval Application for its test to quantitate HCV virus RNA.

About Hepatitis B

According to the World Health Organization, HBV is the most serious type of viral hepatitis infecting 2 billion people each year and representing a serious public health problem. Even with a Hepatitis B vaccine, which has been available since 1982, the U.S. Centers for Disease Control estimates that 1.25 million people are living with chronic Hepatitis B infection. Another 60,000 people become newly infected each year and 5,000 people die from hepatitis B-related complications.

The Hepatitis B virus is spread through having unprotected sex, by sharing drugs, needles, or from an infected mother to her baby during birth. Symptoms occur in about 70 percent of patients which include jaundice, fatigue, abdominal pain, loss of appetite, nausea, and vomiting.

About Roche and the Roche Diagnostics Division

Headquartered in Basel, Switzerland, Roche is one of the world's leading research-focused healthcare groups in the fields of pharmaceuticals and diagnostics. As the world's biggest biotech company and an innovator of products and services for the early detection, prevention, diagnosis and treatment of diseases, the Group contributes on a broad range of fronts to improving people's health and quality of life. Roche is the world leader in in-vitro diagnostics and drugs for cancer and transplantation, and is a market leader in virology. It is also active in other major therapeutic areas such as autoimmune diseases, inflammatory and metabolic disorders and diseases of the central nervous system. In 2007 sales by the Pharmaceuticals Division totaled 36.8 billion Swiss francs, and the Diagnostics Division posted sales of 9.3 billion francs. Roche has R&D agreements and strategic alliances with numerous partners, including majority ownership interests in Genentech and Chugai, and invested over 8 billion Swiss francs in R&D in 2007. Worldwide, the Group employs about 80,000 people. Additional information is available on the Internet at <http://www.roche.com>.

(1) U.S. Centers for Disease Control. <http://www.cdc.gov>

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Down-staged Liver Cancer Associated With Good Post-transplant Outcomes

<http://www.sciencedaily.com>

ScienceDaily (Sep. 4, 2008) — Patients with liver cancer can become viable candidates for transplantation if their tumors respond to treatment, a new study suggests.

For patients with liver cancer (also known as hepatocellular carcinoma), transplantation has been restricted to those who fit the Milan criteria. Their tumors must involve one lesion less than or equal to five centimeters in diameter, or two to three lesions each less than or equal to three centimeters. However, studies have suggested that patients with slightly larger lesions may also do well with a transplant.

Rather than expand the Milan criteria, researchers have suggested down-staging hepatocellular carcinoma to select for tumors with more favorable biology that will respond to treatment and do well following liver transplantation. The impact of successful down-staging on post-transplant outcomes was heretofore unknown.

Researchers, led by Francis Yao of the University of California at San Francisco, conducted a prospective study of down-staging protocol and report intention-to-treat survival, dropout and post-transplant tumor recurrence, along with factors that may influence response to down-staging treatment.

Between June 2002 and January 2007, the researchers enrolled 61 liver cancer patients whose tumor stage exceeded the Milan criteria. Fifty-five of these patients received a combination of laparoscopic radiofrequency ablation (RFA) and transarterial chemoembolization (TACE). The remaining 6 patients underwent resection as the down-staging procedure.

Down-staging was successful in 43 of the 61 patients (70.5 percent), and 35 of those received a liver transplant after a median of 8.2 months. While two of the transplant recipients died (one from graft problems and the other from recurrent hepatitis C infection), the remaining 33 were alive and free of liver cancer recurrence after a median follow-up of 25 months.

In the patients for whom down-staging was unsuccessful, 15 had tumor progression, while 3 died (two related to the down-staging, the other not.)

Comparing the clinical characteristics of the 35 patients who received a liver transplant to the 18 patients with treatment failure, only median alpha fetoprotein (AFP) level was significantly different. Treatment failure was the eventual outcome in seven of the eight patients with pre-treatment AFP > 1000 ng/mL. "High AFP may be a marker for vascular invasion or extra-hepatic disease that escapes detection by conventional imaging techniques," the authors suggest.

The authors note the heterogeneity of they loco-regional therapy may be a weakness of their study, and that the optimal treatment should be determined on a case-by-case basis. They also point out that 25 months of post-transplant follow-up may be too short to fully determine the risk of liver cancer recurrence.

Still, they conclude, "our results suggest that tumor down-staging to meet conventional criteria for orthotopic liver transplantation (OLT) among carefully selected patients is associated with excellent post-transplant outcome. Down-staging put selection pressure against aggressive tumors that are likely to progress despite treatment, whereas tumors with more favorable histology are more likely to respond to treatment and do well after OLT."

They call for further studies to refine down-staging treatment strategies to improve the intention-to-treat outcome.

Journal reference:

Yao et al. Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: An intention-to-treat analysis. *Hepatology*, 2008; 48 (3): 819 DOI: 10.1002/hep.22412

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Hepatitis C Expert Column: New Directions in Hepatitis C Therapy: A Look at the Evolving Therapeutic Arsenal

www.medscape.com

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Introduction

Chronic hepatitis C continues to be the most important cause of chronic liver disease in the United States, potentially resulting in cirrhosis, hepatocellular carcinoma, and the need for liver transplantation. The only US Food and Drug Administration-approved treatment for hepatitis C is combination therapy with pegylated interferon alfa and ribavirin (standard of care), which leads to a sustained virologic response (SVR) in approximately 80% of patients infected with hepatitis C virus (HCV) genotype 2, approximately 60% to 65% infected with genotype 3, and approximately 40% of patients infected with HCV genotype 1.[1-3] If SVR is achieved, durable response is quite likely, providing patients with an excellent chance for long-term viral eradication.

In addition to a relatively low SVR rate in HCV genotype 1 patients, other challenges associated with the current anti-HCV treatment regimen are its side effects and the required duration of therapy, both of which interfere with patients' adherence to the full course of antiviral therapy. In fact, recent reports suggest that the inability to maintain the optimal dose of both pegylated interferon alfa and ribavirin, especially early in the course of treatment, is associated with a lower rate of response to the current standard of care therapy.[3] This may explain, in part, the difference between response rates reported in randomized clinical trials (indicating the efficacy of treatment) compared with the response rates reported in clinical practices (indicating the effectiveness of treatment). To overcome these challenges, recent investigations have focused on optimal management of treatment-associated side effects such as anemia and depression.[1-3]

In addition to managing side effects, research has also focused on developing models to predict low response probability in an effort to avoid futile treatment, and high response probability in an effort to support a full regimen for patients likely to achieve viral eradication. These predictive models are based on viral kinetic data at weeks 4, 12, and 24. Patients who achieve rapid virologic response (RVR; undetectable HCV RNA [< 10 IU/mL] by polymerase chain reaction [PCR] after 4 weeks of treatment) have an excellent chance of achieving SVR.[1,2] In contrast, failure to achieve an early virologic response by week 12 of treatment (a minimum of 2-log drop in HCV RNA from the baseline value) is a reliable negative predictor of response to this combination therapy regimen.[1,2] Furthermore, patients who continue to have detectable virus after 24 weeks of therapy are unlikely to achieve SVR and are considered "nonresponders" to combination therapy.

Although findings on viral kinetics and adherence can help clinicians individualize therapy and maximize SVR, many patients, especially those infected with HCV genotype 1, fail to respond to the current standard-of-care treatment. This has led to the development of new strategies and medications for HCV treatment. Although a number of approaches are under consideration, 3 strategies appear most promising: (1) improving the pharmacokinetics and side-effect profile of

interferon; (2) improving the pharmacokinetics and side-effect profile of ribavirin; and (3) targeting viral enzymes required for HCV viral replication. This report discusses the most recent findings with regard to these new approaches to the treatment of HCV infection, with special focus on specifically targeted antiviral therapy for hepatitis C (STAT-C) regimens.[4,5]

New Interferon Preparations

Given the required weekly injections of pegylated interferon alfa and its associated side effects, several agents have been developed to reduce the injection frequency. These include albinterferon, controlled-release recombinant interferon alfa, maxy-alfa interferon, oral interferon, and implantable mini-pump technology to deliver continuous interferon infusion.

Albinterferon* was developed by genetically fusing human albumin to interferon alfa. The concept is that this recombinant agent will have a longer sustainable half-life and thus allow a reduction in the frequency of interferon administration. Results from phase 2 clinical trials using 900-1200 mcg of albinterferon every 2 weeks in addition to weight-based dosing of ribavirin suggested similar efficacy but better health-related quality of life when compared with the standard combination regimen.[6] Additional phase 3 clinical trials of this agent for the treatment of hepatitis C are currently ongoing.

Controlled-release recombinant interferon alfa* was developed as a biodegradable polymer delivery system for interferon alfa-2b. In early phase clinical trials, this novel interferon delivery system was administered every 2 weeks, and preliminary data suggest good pharmacokinetics and fewer side effects. The safety and efficacy of this drug are still under investigation.[5,7]

Maxy-alfa interferon* has been developed with molecular biological techniques to improve the immunomodulatory effect of interferon alfa. Although preclinical data suggested enhanced antiviral effects in cell cultures, subsequent phase 1 clinical trial data were not encouraging.[5]

Oral long-lasting interferon alfa* is another novel variant that seems to be more resistant to proteolytic degradation. In preclinical studies in animal models, oral administration resulted in good pharmacokinetics and safety profiles.[5,8] Nevertheless, data from phase 1 clinical trials of this agent in humans are not yet available.[5,8]

Finally, implantable mini-pumps are being developed to deliver interferon alfa or more potent forms of interferon, such as interferon omega. These mini-pumps* are used to infuse and deliver a steady flow of interferon to HCV-infected patients. Some of the mini-pumps must be changed every 3 months to remain functional.[5,9] Although promising, data on these mini-pump technologies for interferon infusion in humans are not yet available.

As delivery systems and side-effect profiles for interferon preparations improve, HCV-infected patients will be able to be provided with more efficient options for antiviral therapy.

Ribavirin-Like Drugs

The efficacy of standard interferon alfa or pegylated interferon alfa improves significantly with the addition of ribavirin. As mentioned, the combination of these 2 drugs represents the current standard of care for the treatment of hepatitis C. Furthermore, preliminary studies using newer, targeted treatment for HCV suggest that both pegylated interferon alfa and ribavirin remain an essential part of a triple-drug combination regimen (as will be discussed later). In addition to

enhancing the efficacy of pegylated interferon alfa, the addition of ribavirin to the treatment regimen also increases the side effects associated with combination therapy. The most important side effect of ribavirin is anemia, which is predominantly related to a hemolytic process. Another therapeutic agent, taribavirin,* an oral prodrug of ribavirin, was developed in an attempt to reduce this potentially serious side effect. Taribavirin, previously known as viramidine, is taken up preferentially by the liver and converted to ribavirin. Because of this hepatic preference, taribavirin is theoretically associated with a lower risk for anemia. Two large randomized clinical trials[10,11] compared the efficacy of 800-, 1200-, or 1600-mg daily doses of taribavirin with 1000- or 1200-mg daily doses of ribavirin, given in combination with pegylated interferon alfa, in treatment-naïve chronic hepatitis C patients. Both studies showed that taribavirin was associated with lower rates of anemia as well as lower SVR rates. Data from clinical trials using higher doses of taribavirin in combination with pegylated interferon are not available.

Drugs Targeting Viral Enzymes

The current treatment regimens for HCV infection act predominantly through immunomodulatory mechanisms. Newer anti-HCV drugs in development, however, target several viral enzymes such as the NS3/4A serine protease, NS5B RNA-dependent RNA-polymerase, and, most recently, the cyclophilin proteins.

It is important to remember the ability of HCV to develop escape mutants. Mutations are common because the virus has a high rate of replication without a good repair mechanism. These mutations form the basis of the "escape mutants," which allow HCV to escape innate immunity and to resist the action of antiviral drugs.[12] In a similar fashion, the use of monotherapy with new drugs designed to target HCV viral enzymes is expected to result in the development of viral resistance and the failure of these novel therapeutic agents as monotherapy. It is almost certain that in the near future, multidrug regimens will be required for the antiviral treatment of HCV infection using these targeted agents.

The most exciting group of anti-HCV therapies on the horizon are known as the STAT-C agents. These drugs are based on the model of antiretroviral therapy for HIV infection. Investigators had to overcome many challenges to develop the required targets for these therapeutic agents, including the need for a detailed knowledge of the hepatitis C replication cycle, development of an effective replication cell culture system or HCV replicon system, and a 3-dimensional structure analysis of important HCV enzymes (ie, the NS3/4A protease and NS5B polymerase). The following sections discuss the development of these agents and their potential role in the treatment of HCV infection.[4,5,13,14]

Protease Inhibitors

BILN-2061 (ciluprevir). BILN-2061,* a potent inhibitor of the NS3/4A protease, was tested in a phase 1 clinical trial and showed a rapid reduction in viral load within the first 48 hours.[15] Although BILN-2061 demonstrated potent antiviral activity against HCV genotype 1, the virologic response was less pronounced and more variable in HCV genotypes 2 and 3. Despite its potent antiviral effect, further development of this agent was halted because of concerns for potential cardiotoxicity seen in rhesus monkeys treated with higher doses of the drug for 4 weeks' duration.

VX-950 (telaprevir). Telaprevir* is a selective and potent inhibitor of the HCV NS3/4A serine protease. In a phase 1 clinical trial, patients with HCV genotype 1 were randomized to placebo or telaprevir monotherapy at doses of 450 mg or 750 mg every 8 hours or 1250 mg every 12 hours for 14 days.[16] The majority of patients (79%) in this clinical trial had failed to respond (did not achieve SVR) to previous treatment to interferon-based regimens for hepatitis C. After 14 days of treatment, telaprevir administered at a dose of 750 mg every 8 hours resulted in a 4.4-log decline in HCV RNA from baseline. At 450 mg and 1250 mg per day dosing, the maximum viral suppression occurred at days 3 and 7. However, a subsequent increase in HCV RNA was attributed to the development of resistant variants of HCV. Subsequent analysis[16] examined the efficacy of combining telaprevir with pegylated interferon alfa-2a. In this study, one cohort of subjects received telaprevir in combination with pegylated interferon alfa-2a for 14 days. At the end of the 14-day study period, a 5.5-log decline in HCV RNA was observed. Indeed, 75% of patients had undetectable HCV RNA (< 30 IU/mL) by day 14 of treatment. After the completion of 14 days of the study period, in an off-study follow-up protocol, all patients were given a combination of pegylated interferon alfa-2a and ribavirin for another 24 weeks.[16] Nineteen of 20 patients who had originally received telaprevir monotherapy or telaprevir and pegylated interferon in combination continued standard combination therapy with pegylated interferon/ribavirin. At week 24, all patients became HCV RNA undetectable, which was sustained in 61%. These studies led to the development of triple combination protocols, involving telaprevir, ribavirin, and pegylated interferon alfa, which were tested in 2 large randomized clinical trials (PROVE 1 and PROVE 2).

PROVE 1, conducted in the United States, is a randomized, double-blind, placebo-controlled, clinical trial assessing the safety and efficacy of telaprevir 750 mg daily (given every 8 hours) in combination with pegylated interferon alfa-2a and ribavirin in patients with treatment-naive HCV genotype 1.[17] The duration of treatment in this study ranged from 12 to 48 weeks. After 12 weeks of the triple-therapy regimen, pegylated interferon/ribavirin only was continued for 0, 12, or 36 weeks; the control group received the current standard of care (48 weeks of pegylated interferon/ribavirin). Patients randomized to the treatment arms receiving 12 or 24 weeks of therapy were eligible to stop treatment if they achieved an RVR at week 4 and maintained this response at weeks 10 and 20. Otherwise, all subjects received a full 48-week course of therapy. Interim analysis of this study showed an RVR rate of 79% in the triple therapy arm (vs 11% in the standard of care arm), and a week-12 virologic response (HCV RNA < 10 IU/mL) was seen in 70% of patients in the triple combination arm (vs 39% in the standard of care arm). This study also showed that the majority (67%) of patients who achieved RVR and discontinued treatment at week 12 maintained a virologic response 20 weeks after discontinuing treatment.

These findings support the notion that protease inhibitors, such as telaprevir, when used in a triple combination regimen in a select group of patients (those achieving RVR), may shorten the course of treatment. Although the total incidence of adverse events was similar in the triple combination and standard therapy arms, the triple combination arm had more discontinuations (11% vs 3%) and higher rates of gastrointestinal side effects and anemia. Final results of PROVE 1 and PROVE 2 are currently pending.[18-22]

PROVE 2, conducted primarily in European centers, had a study design similar to PROVE 1 but included an arm that received telaprevir + pegylated interferon without ribavirin.[23] In general, the results were similar to those of PROVE 1: the triple therapy arm resulted in significantly greater virologic response than standard therapy at 4, 12, and 24 weeks. However, patients in the

treatment arm that received telaprevir/pegylated interferon without ribavirin were less likely to suppress HCV RNA and more likely to relapse than those who received the triple combination regimen.

PROVE 3 is an ongoing phase 2b study evaluating telaprevir-based therapy in patients with genotype 1 chronic hepatitis C who did not achieve an SVR with prior standard-of-care therapy. Results are pending. In addition, several phase 3 randomized, controlled trials are also being initiated to further establish the efficacy and safety of this triple therapy regimen (telaprevir/pegylated interferon/ribavirin) in HCV genotype 1, treatment-naïve (ADVANCE [A New Direction in HCV Care: A Study of Treatment-Naïve Hepatitis C Patients With Telaprevir]) and nonresponder (REALIZE [Re-treatment of Patients With Telaprevir-based Regimen to Optimize Outcomes]) patients.

SCH503034 (boceprevir). Boceprevir* is another NS3 serum protease inhibitor. In a phase 1 clinical trial, 61 patients infected with HCV genotype 1 who were nonresponders to previous treatment with pegylated interferon alfa-based therapy were randomized to regimens with a variable duration sequence of boceprevir monotherapy or a combination of pegylated interferon alfa-2b and boceprevir at different doses (200 mg thrice daily or 400 mg thrice daily).[24] This study showed that after 14 days, the combination of pegylated interferon alfa 2b and boceprevir given at a dose of 200 or 400 mg thrice daily was associated with an approximately 2.45 and 2.88-log drop in HCV RNA from baseline.

In addition, several clinical trials assessing the efficacy of boceprevir in a triple combination regimen are being conducted in HCV genotype 1 patients who are interferon-naïve and in patients who are considered nonresponders to previous treatment.[4,5] SPRINT-1 (Serine Protease Inhibitor Therapy-1),[25] a phase 2 randomized clinical trial conducted in HCV treatment-naïve genotype 1 patients, showed that HCV RNA was undetectable in more than 73% of those who received the triple therapy of boceprevir plus pegylated interferon and ribavirin at week 12 after initiation of treatment, compared with only 34% of the control group (who received standard doses of pegylated interferon and ribavirin). The treatment was tolerated well overall, although anemia was more common in the triple-therapy arm.

Other protease inhibitors. The antiviral activity of another HCV protease inhibitor, ACH-806 (also known as GS-9132),* has been tested in a phase 1 clinical trial.[26] Preliminary analysis suggests that ACH-806 is associated with a 2.38-log decline in HCV RNA within 5 days of initiating therapy. However, the analysis also showed a reversible increase in serum creatinine, resulting in the halting of further development of this agent. Finally, ITMN-191* is another HCV NS3/4A protease inhibitor that has been tested in replication model(s).[27] Phase 1 clinical trials with this agent were recently completed, but additional dosing studies are ongoing.

HCV RNA Polymerase Inhibitors

Another group of viral enzyme inhibitors comprise those agents that inhibit the HCV RNA-dependent RNA polymerase. Two classes of polymerase inhibitors are currently under development: nucleoside and nonnucleoside analogs.

Nucleoside analog polymerase inhibitors. NM283 (valopicitabine)* is a ribonucleoside analog that targets the viral RNA polymerase and is a viral RNA chain terminator. The efficacy and safety of valopicitabine alone or in combination with pegylated interferon alfa were assessed in

phase 1 and 2 clinical trials. In patients with HCV genotype 1 who were nonresponders to previous treatment, combination therapy with pegylated interferon + valopicitabine 800 mg daily resulted in a 3.32-log reduction in HCV RNA after 24 weeks of treatment. In another study assessing this combination in treatment-naïve HCV genotype 1 patients, 4.56- and 4.41-log reductions in HCV RNA were noted after 24 and 36 weeks of treatment, respectively. Both trials required protocol amendments that reduced the dose of valopicitabine to 400 mg daily. At the end of 48 weeks of therapy, the efficacy was not significantly different from the standard-of-care therapy, although more frequent dose-dependent gastrointestinal side effects were noted. In fact, the higher dose of valopicitabine was associated with more significant side effects, specifically nausea and vomiting. Because of the gastrointestinal side-effect profile of valopicitabine and lack of clear gains in terms of efficacy, further development of this compound has been suspended.[28-30]

A prodrug of R1479 and a potent inhibitor of the NS5B-RNA-dependent HCV RNA polymerase, R1626* is also being developed as a STAT-C agent. R1626 is an oral nucleoside analog that has been administered at doses ranging from 500 mg to 4500 mg twice daily for 14 days in treatment-naïve HCV genotype 1 patients. The largest mean reduction in serum HCV RNA of 3.7 logs was observed with the 4500-mg twice daily dose of R1626.[31,32] Additionally, recent data reported in treatment-naïve HCV genotype 1 patients showed that 84% of patients who received triple therapy of R1626/pegylated interferon/ribavirin had undetectable HCV RNA at the end of treatment vs 65% who received standard treatment with pegylated interferon and ribavirin.[33] Neutropenia (dose-dependent) was common in patients receiving R1626.

Nonnucleoside analog inhibitors. Several nonnucleoside analog inhibitors are also being developed. The mechanism of action of these drugs is different from that of the nucleoside analogs; therefore, cross resistance is unlikely.[4,5]

The nonnucleoside polymerase inhibitor HCV-796* was studied in a phase 1 clinical trial at doses ranging from 50 mg per day to 1500 mg per day. Monotherapy trials of HCV-796 showed a 1.4-log decline in the HCV RNA viral load in patients receiving the higher doses of drug. Phase 2 clinical trials using a combination of HCV-796 and pegylated interferon alfa showed a mean viral reduction of 3.3 to 3.5 logs after 14 days of treatment. Subsequent phase 2 clinical trials of this agent were carried out in combination with pegylated interferon alfa-2a with or without ribavirin in both treatment-naïve and nonresponder patients. Clinically significant elevations in liver enzyme levels were noted, resulting in discontinuation of further development of this compound as a potential treatment option for HCV infection.[4,5,34]

Other protease/polymerase inhibitors. In addition to the protease and polymerase inhibitors described in this section, a number of other agents (protease inhibitors: ACH-1095;* polymerase inhibitors: PSI-6130,* R7128,* GS-9190,* BILB 1941,* A-831,* and A-689*) have also undergone testing in early phase clinical trials. The findings regarding these agents are preliminary and await additional analysis.[4,5]

Cyclophilin Inhibitors

Cyclophilins are proteins widely found in human cells; they are involved in protein folding and stimulate the activity of the HCV NS5B-polymerase. The cyclophilin inhibitor DEBIO-25* has demonstrated antiviral effects against both HCV and HIV.[35] The safety and efficacy of this class of drugs is currently pending.

Conclusion

We have witnessed many advances in our understanding of the life cycle of HCV and the enzymes critical for its replication over the past decade. Although efforts to optimize the current immunomodulatory therapy for HCV (pegylated interferon and ribavirin) have continued, newer, targeted treatments for HCV are being developed. It is becoming increasingly clear that these enzyme inhibitors are most effective when used in combination with the current standard of care, combination pegylated interferon and ribavirin. However, triple combination therapy regimens may not only enhance efficacy but also shorten the course of therapy. Current findings regarding the STAT-C class of agents suggest that protease inhibitors are at a more advanced stage of clinical development than polymerase inhibitors. Additionally, newer treatment options using cyclophilin inhibitors may provide further targets for combating hepatitis C infection. Nevertheless, clinical trials of these drugs suggest that their efficacy may increase along with the side-effect profile when used in these multidrug cocktails. It is important to balance increased efficacy and shorter treatment duration with increased toxicity and costs associated with additional drugs and toxicity monitoring. With these enthusiastic but cautious notes, we expect the next decade to bring tremendous advances in the treatment of HCV infection. Nevertheless, in achieving these advances, the safety, efficacy, and effectiveness of these drugs must be established in addition to their cost effectiveness and positive impact on health-related quality of life.

*The US Food and Drug Administration has not approved this medication for this use.

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References

http://www.medscape.com/viewarticle/579324_print