

HCV ADVOCATE WEEKLY NEWS REVIEW

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

*Alan Franciscus
Editor-in-Chief*

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Sep 8, 2008

Hepatitis C Battle Intensifying

<http://www.lvrj.com>

By Annette Wells
Review-Journal

Liver specialists in Nevada are seeing an increase in patients since health officials in February announced an outbreak of hepatitis C cases linked to an endoscopy clinic.

Dr. Robert Gish, a California physician who has had a part-time practice in Nevada for the past two decades, said his patient load has doubled since the outbreak was made public. Some of his new patients underwent procedures at the 700 Shadow Lane facility and have tested positive for hepatitis C. Other patients are just learning they have the disease and are seeking treatment, Gish said.

Dr. Donald Hillebrand, another liver specialist from California with a part-time Nevada practice, said his patient load "has picked up substantially."

Hillebrand was hired by Southwest Medical Associates in April to help with an anticipated growth in liver patients as a result of the outbreak, linked to the Endoscopy Center of Southern Nevada, 700 Shadow Lane.

Hillebrand said he is seeing two general types of liver patients in Southern Nevada. One group is composed of those with end-stage liver disease; the other consists of general hepatology patients, those with hepatitis C or B or who just need a liver doctor.

"I've seen a few individuals that were patients of the Endoscopy Center. Some of them have reasons for liver disease independent of the procedures. It is going to be a difficult task for someone to sort that out, to determine whether they got the disease at the clinic versus another time in life," Hillebrand said.

"We are talking to patients about that aspect, and it is frustrating. It is frustrating for the patients, and it is frustrating for us. ... What we tell our patients is, while it would be helpful to know the source, you have to move forward."

That entails a liver specialist evaluating how much of problem hepatitis C is going to be for the patient, he said.

How treatable hepatitis C will be is strongly influenced by its strain, liver function and the patient's overall health. For many, losing weight through diet and exercise and abstaining from alcohol might be all they need.

Some patients will need to receive ribavirin and interferon, drugs known more for their side effects than effectiveness.

"It was brutal," said Paul Lorenz, a patient of Gish who spent 66 weeks undergoing interferon treatment.

"It was pills in the morning, pills at night and an injection once a week. ... It was like having the worst flu you've ever had multiplied by 10. Aches, fevers, chills, sweat and a lot of time thinking crazy things. Everything they said would happen happened."

Lorenz, an Air Force veteran, thinks his blood could have been tainted by inoculations during his deployment to Vietnam. Lorenz said he was so angry he could kill when he found out he had

hepatitis C. He was not a patient of the Endoscopy Center or its affiliated clinic on Burnham Avenue that also was linked to hepatitis transmission.

Fortunately for Lorenz, an electrician, he is among the 50 percent of patients for which interferon works.

The virus has been undetectable in his blood for two years.

The same can't be said for another Gish patient, Raymond Sword, 55.

Sword, who said his hepatitis C could have been the result of drug use in the '70s and '80s, was diagnosed seven years ago after a routine physical exam. He began interferon treatments a few years later, which he calls "the worst thing that ever happened" to him.

Sword, a shuttle bus driver, ended up with cirrhosis, which eventually led to end-stage liver disease. On May 13, he had a liver transplant at California Pacific Medical Center in San Francisco.

Sword still has hepatitis C.

"Treatment for hepatitis C has come a long way; the bad news is we still have a ways to go," said Hillebrand, medical director of Scripps' Center for Organ and Cell Transplantation in San Diego. "There are still things we just don't know about treatment."

In some cases, patients with acute hepatitis C have "cleared" the disease on their own, Hillebrand said.

The term acute hepatitis refers to the six-month period of time after the virus has entered the body and antibodies can be detected.

In about half of the acute hepatitis C cases, patients' immune systems are able to clear the disease, both doctors said.

"Hepatitis C is curable. You just have to know you have it and get treatment," said Gish, medical director of San Francisco's Pacific Medical Center's liver transplant program.

"This is a situation where there's much awareness about liver disease, so more people are getting tested for it. If ever there was anything positive from this outbreak, it is that there is more awareness about liver disease."

In February, the Southern Nevada Health District announced that six people had contracted hepatitis C and that they all had undergone procedures at the Endoscopy Center's Shadow Lane facility.

An investigation by the Centers for Disease Control and Prevention and health district revealed that the reuse of syringes in a manner that contaminated vials of medication, and the reuse of those vials intended for a single patient, had exposed patients to hepatitis B and C and HIV.

Notifications were sent to more than 60,000 former patients of the Shadow Lane facility, as well as its Desert Shadow Endoscopy Center affiliate, urging them to get tested for the blood-borne viruses.

Health officials have not linked any HIV or hepatitis B cases to either of the two facilities; eight hepatitis C cases are linked to the Shadow Lane facility and one to the Burnham facility.

About 400 former patients of the Shadow Lane facility have tested positive for hepatitis C. Health officials have said 77 of them are "possibly" linked to that clinic.

In June, the health district set up a hepatitis C exposure registry to help identify patients who had procedures at the two clinics. A little more than 7,000 former patients -- 75 percent from Shadow Lane and 25 percent from Burnham -- have responded to the registry, said Brian Labus, senior epidemiologist.

While 95 percent of the patients are from Southern Nevada, registry respondents come from 43 states, Labus said. Their average age is 65.

Labus said 91 percent of the former patients reported no risk factors other than having a procedure done at the endoscopy center. Nine percent of the respondents reported having at least one risk factor.

"After hearing about the hepatitis C outbreak, I thought about whether I had ever went to any of those clinics," said Sword, a father of two teenagers.

"I never had, but it saddens me to know that a whole lot of people may have this awful disease because they did nothing other than go to the wrong place."

Contact reporter Annette Wells at awells@reviewjournal.com or 702 383-0283.

Support for needle exchange

<http://www.modbee.com>

Recently the Stanislaus County civil grand jury wrote in support of syringe exchange in Stanislaus County. These programs curtail the spread of hepatitis C, HIV and other blood-borne diseases.

Hepatitis C and HIV are spread very easily among people who do not have these diseases, if they choose to share a needle with someone, even once. For infected and diagnosed individuals, disease treatment comes from taxpayers.

The grand jury recognized this public health and fiscal threat. Even the law enforcement executives supported a syringe exchange program. Now those law enforcement executives want to reverse that position.

I submit that the Board of Supervisors' inaction will result in consigning hundreds more people to acquiring hepatitis C, HIV and other blood-borne pathogenic diseases through needle-sharing

behavior over the next 12 months, costing lives and dollars that Stanislaus County can ill afford. As well, the infected and arrested can transmit disease again and again.

The responsible, most conservative, most compassionate approach to this issue is to prevent disease through syringe exchange programs.

Please call your county supervisor and indicate your support for a syringe exchange program in this county. It's a matter of someone's life -- maybe yours.

ELIZABETH VENCILL

Modesto

Editor's note: Vencill served on the 2007-08 grand jury that made this recommendation.

Pharmasset Reports Preliminary Results of a 4-week Proof-of-Concept Combination Study of R7128

www.pharmalive.com

- 90% of genotype 2 or 3 patients achieve undetectable HCV RNA levels following 4 weeks of treatment with R7128 1500mg BID with Pegasys(R) plus Copegus(R) -

PRINCETON, N.J., September 08, 2008 /PRNewswire-FirstCall/ -- Pharmasset, Inc. announces the preliminary results of the fourth cohort of a 4-week Phase 1 proof-of-concept clinical trial evaluating R7128 1500mg twice daily (BID) in combination with the standard of care (SOC), Pegasys(R) (pegylated interferon) plus Copegus(R) (ribavirin) in 20 patients chronically infected with hepatitis C virus (HCV) genotype 2 or 3 who had not achieved a Sustained Viral Response (SVR) with prior SOC therapy. R7128, a prodrug of PSI-6130, is a nucleoside analogue polymerase inhibitor of HCV that is being developed through Pharmasset's collaboration with Roche.

In this study, preliminary results indicated that R7128 demonstrated significant short-term antiviral activity in patients who were previous non-responders or relapsers to treatment and was generally safe and well tolerated. Of the 25 patients enrolled, 20 patients received R7128 1500mg BID and 5 received placebo. Patients receiving R7128 1500mg BID with SOC for 4 weeks achieved a mean 5.0 log₁₀ HCV RNA decline and 90% (18 of 20) achieved undetectable (<15 IU/ml) HCV RNA levels (RVR). Patients receiving placebo with SOC for 4 weeks achieved a mean 3.7 log₁₀ HCV RNA decline and 60% (3 of 5) achieved an RVR. These viral load reductions for patients with genotype 2 or 3 are similar to those reported earlier for patients with genotype 1 treated with 1000mg BID and 1500mg BID and are consistent with the in vitro data demonstrating equal potency by R7128 against HCV genotypes 1, 2, 3 and 4.

The preliminary safety and tolerability of R7128 1500mg BID with SOC was comparable to placebo with SOC in Cohort 4.

Dr. Michelle Berrey, Pharmasset's Chief Medical Officer stated, "In this study, R7128, in combination with SOC, has demonstrated significant antiviral activity in genotype 2 or 3 patients

who had failed prior interferon-based therapy. R7128, an HCV nucleoside polymerase inhibitor, may provide better antiviral activity in these patients where the protease inhibitors and non-nucleoside polymerase inhibitors have not yet shown success. Longer-term studies of R7128 with SOC are needed to provide additional information about its potential to improve SVR rates and possibly shorten the treatment duration for genotype 2 or 3 HCV patients."

"Patients with genotype 2 or 3 represent 20-30% of the worldwide chronically infected HCV population. Up to 40% of these patients, using SOC in first line therapy for 24 weeks, do not achieve an SVR, which represents an unmet medical need that R7128 has the potential to address," stated Patrick Higgins, Pharmasset's Executive Vice President of Sales and Marketing. "R7128 is the first small molecule to demonstrate significant antiviral activity in humans against a broad spectrum of HCV genotypes. If this early evidence of competitive advantage is sustained in future development, this potentially means that R7128 could become the preferred direct-acting antiviral to be added to the SOC because it is equally active across all of the most common genotypes and has a high barrier to drug resistance."

R7128 4-week Combination Study Overview

The 4-week Phase 1 combination clinical trial was a multiple center, observer-blinded, randomized and placebo-controlled study that was conducted in 81 treatment-naive patients chronically infected with HCV genotype 1 and 25 prior treatment non-responder patients chronically infected with HCV genotype 2 or 3. The primary objective was to assess the safety, tolerability, pharmacokinetics and antiviral activity of R7128 in the clinically-relevant setting of combination therapy for chronic HCV infection. Cohort 1 administered R7128 500mg BID, Cohort 2 administered R7128 1500mg BID, and Cohort 3 administered an intermediate dose of 1000mg BID, all given in combination with pegylated interferon and ribavirin for 28 days. All subjects then went on to receive a total of 48 weeks of the standard-of-care regimen. In Cohort 4, patients with HCV genotype 2 or 3 who did not achieve an SVR with previous interferon-based therapy were administered R7128 1500mg BID in combination with SOC for 4 weeks, and subsequently treated with an additional 20 weeks of SOC.

About R7128

R7128 is being developed for the treatment of chronic HCV infection. R7128 is a prodrug of PSI-6130, a cytidine nucleoside analog inhibitor of HCV RNA polymerase. A prodrug is a chemically modified form of a molecule designed to enhance the absorption, distribution and metabolic properties of that molecule. R7128 has shown in vitro activity against all of the most common HCV genotypes (1, 2, 3 and 4).

Results from an oral single ascending dose study of PSI-6130 in 24 healthy male volunteers showed that PSI-6130 was generally well tolerated with no serious adverse events in doses up to 3000 mg.

R7128 demonstrated significant, dose-dependent antiviral activity across four prior treatment-failure patient cohorts (n=40) receiving 750 mg or 1500 mg administered either once-daily or twice-daily for 14 days as monotherapy. The greatest mean decrease in HCV RNA from baseline was demonstrated in the patient cohort that received 1500 mg twice-daily, the highest dose of R7128 administered in the study. These patients demonstrated a mean 2.7 log₁₀ IU/mL (>99%) decrease in HCV RNA. There was no evidence of the development of viral resistance in any dose cohort after 14 days of dosing.

In a 4-week Phase 1 combination study that was conducted in 81 treatment-naive patients chronically infected with HCV genotype 1, R7128 demonstrated significant short-term antiviral activity with safety and tolerability comparable to placebo with SOC. Results from the 500mg, 1500mg and 1000mg dose cohorts (cohorts 1, 2 and 3) in 81 treatment-naive patients chronically infected with HCV genotype 1 indicated:

- Preliminary results with R7128 1000mg BID with SOC indicated patients achieved a mean 5.0 log₁₀ IU/mL decrease in HCV RNA and 88% (22 of 25) patients achieved RVR.
- Results with R7128 1500mg BID with SOC indicated patients achieved a mean 5.1 log₁₀ IU/mL decrease in HCV RNA and 85% (17 of 20) patients achieved RVR
- Results with R7128 500mg BID with SOC indicated patients achieved a mean 3.8 log₁₀ IU/mL decrease in HCV RNA and 30% (6 of 20) patients achieved RVR.
- Results with placebo with SOC indicated patients achieved a mean 2.9 log₁₀ IU/mL decrease in HCV RNA and 18.75% (3 of 16) patients achieved RVR

About Pharmasset

Pharmasset is a clinical-stage pharmaceutical company committed to discovering, developing and commercializing novel drugs to treat viral infections. Pharmasset's primary focus is on the development of oral therapeutics for the treatment of hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV).

Pharmasset is currently developing three product candidates. Clevudine, for the treatment of chronic HBV infection, is enrolling Phase 3 clinical trials for registration in North, Central and South America and Europe. Clevudine is already approved for HBV in South Korea and marketed by Bukwang Pharmaceuticals in South Korea under the brand name Levovir. R7128, an oral treatment for chronic HCV infection, is in a 4-week Phase 1 clinical trial in combination with Pegasys(R) plus Copegus(R) through a strategic collaboration with Roche. Racivir, which is being developed for the treatment of HIV in combination with other approved HIV drugs, has completed a Phase 2 clinical trial.

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Sep 9, 2008

Complications common for living liver donors

www.reuters.com

NEW YORK (Reuters Health) - Thirty-eight percent of liver donors will experience a complication with their surgical procedure, and although in most cases the severity is low grade, a significant proportion of patients will experience a severe or even life-threatening complication, new research shows.

Prior studies that have assessed the complications that living liver donors can develop have been confined to single medical centers, according to the report in the journal Gastroenterology. The

present study addressed this limitation by using data on complications for donors enrolled in the nine-center "Adult-to-Adult Living Donor Liver Transplantation Cohort Study."

Although most liver transplants involve whole livers from recently deceased organ donors, the serious shortage of organs has lead physicians to explore the use of living liver donors. After a portion of this large organ is surgically removed, it usual regenerates in the donor within 4 or 6 weeks. Similarly, the new liver will eventually grow to full size.

A total of 405 donors were accepted for donation between 1998 and 2003, Dr. Rafik M. Ghobrial from the University of California, Los Angeles, and colleagues report. Of these, 393 underwent donation and 12 had an aborted procedure.

Sixty-two percent of the liver donors had no complications, 21 percent had one complication, and 17 percent had two or more, for a total of 220 complications, the researchers found.

The bulk of the complications were minor (48 percent, grade 1) or caused no lasting disability (47 percent, grade 2). However, 4 percent of the complications caused lasting disability (grade 3) and 0.8 percent were fatal (grade 4).

The most common complication, accounting for 12 percent of cases, was bacterial infection, followed by a bile leak (9 percent) and a hernia (6 percent). In two cases, a clot formed in the portal vein.

The hospital readmission rate was 13 percent, and 4 percent of donors required multiple readmissions.

The findings from this study "should be used for the education and informed consent process for potential donors," Ghobrial and colleagues state. "Informed consent" is the mandatory procedure that requires physicians to fully explain to patients all of the risks and benefits of a procedure or treatment and to inform them of any alternatives, if any.

Efavirenz does not increase risk of depression in those taking hepatitis C treatment

www.aidsmap.com

Michael Carter

Treatment with efavirenz (Sustiva) does not appear to increase the risk of depression for HIV-positive patients coinfectd with hepatitis C virus who are receiving hepatitis C therapy, Spanish researchers report in the September 1st edition of the Journal of Acquired Immune Deficiency Syndromes.

But the researchers did find that treatment with efavirenz increased the risk of mood disorders in coinfectd patients receiving anti-hepatitis C drugs.

Many patients with HIV are also coinfectd with hepatitis C virus. The current standard of care for hepatitis C infection is pegylated interferon with ribavirin. This treatment clears infection with hepatitis C in approximately 66% of coinfectd patients who receive treatment soon after

they are infected with hepatitis C and in about a third of coinfecting patients who have chronic hepatitis C infection.

Pegylated interferon can cause significant side-effects, including symptoms of depression, headache and insomnia. Such symptoms, as well as other neuropsychiatric side-effects, can also be caused by efavirenz, a drug used for first-line HIV therapy.

Researchers in Madrid wanted to determine the safety of pegylated interferon in patients taking efavirenz. They therefore looked at the medical records of 266 HIV-positive patients coinfecting with hepatitis C virus who received hepatitis C treatment between 1999 and 2006. A total of 53 (20%) of these patients were also receiving treatment with efavirenz. The researchers compared rates of neuropsychiatric side-effects in the efavirenz-treated patients and those seen in patients who did not receive therapy with this drug.

There was a high incidence of neuropsychiatric side-effects, and the investigators noted that there was a trend just short of statistical significance for a higher risk of such side-effects amongst the efavirenz-treated patients (79% vs 65%, $p = 0.051$). Mood disorders, such as sadness and apathy were significantly more common amongst the patients treated with efavirenz (36% vs 23%, $p = 0.046$). However, although efavirenz-treated patients were more likely to have received treatment with antidepressants (23% vs 16%), the difference was not statistically significant.

The investigators found no statistically significant difference in the rate of anxiety, insomnia, irritability, headache, and use of drugs for anxiety or sleeping tablets between the patients treated with efavirenz and those not receiving this drug.

When the investigators restricted their analysis to patients with cirrhosis, they found that patients treated with efavirenz were slightly less likely to report neuropsychiatric side-effects (70% vs 85%, $p = 0.2$). Furthermore, patients taking efavirenz were less likely to report insomnia (15% vs 55%).

Few patients stopped treatment because of side-effects, and the risk of this was not increased by treatment with efavirenz.

The investigators conclude, “although concomitant efavirenz use may favour symptoms of mood disorder, it was not related to an increased risk of significant depression requiring treatment.”

Reference

Quereda C et al. Effect of treatment with efavirenz on neuropsychiatric adverse events of interferon in HIV/HCV-coinfecting patients *J Acquir Immune Defic Syndr* 49: 61 – 62, 2008.

Vertex Fending Off Competitors By Treating the Toughest Patients With Hepatitis C

<http://www.xconomy.com>

Luke Timmerman

Vertex Pharmaceuticals is being chased by a couple of deep-pocketed competitors—Schering-Plough and Roche—in the race to develop the next big thing for patients with the hepatitis C virus. Now Vertex, the Cambridge, MA-based biotech company, thinks it has found a way to fend off the challengers. It intends to show its drug—telaprevir—can cure patients who have failed on previous treatments, as well as those who are just beginning therapy.

Vertex (NASDAQ: VRTX) unveiled this key element of its strategy last month in the design of a 650-patient clinical trial called Realize. The study will look at whether telaprevir can cure a broad swath of hepatitis patients who didn't respond to a prior round of treatment, and thus are in danger of serious liver damage later in life. The patients include those who didn't respond at all to a previous treatment, some who responded partially but not enough, and some who were helped temporarily, but eventually relapsed.

Regulators in the U.S. and Europe allowed Vertex to recruit the hardest cases, known as “null responders” into the clinical trial. Those patients aren't being allowed into a large trial of Schering-Plough's competitor, boceprevir. Vertex was able to get those patients included based partly on promising data from a mid-stage study called Prove 3, which has shown that 52 percent of patients on telaprevir had no evidence of the hepatitis C virus left in the blood for at least three months after completing therapy. Standard treatments given a second time do that well for about 15 percent of patients. That kind of difference in effectiveness means big bucks for telaprevir: an estimated 6 million people in the U.S. and Europe have chronic hepatitis C infections, and about 650,000 have failed on the standard treatment. Telaprevir alone could generate \$2.6 billion in U.S. sales in 2013 when factoring in patients who failed treatment and those who are new to therapy, according to Rachel McMinn, an analyst with Cowen & Co. in San Francisco.

“Vertex's telaprevir will show strong data in treatment-failure patients that significantly outshines prior data for Schering-Plough's boceprevir,” said McMinn, in a note to clients last month, which looks ahead to presentations at the American Association for the Study of Liver Diseases annual meeting in November.

Showing a benefit among the toughest-to-treat patients is important to Vertex, partly because it would appeal to the group of patients who are most motivated to seek new treatment options, and because it could enable the company to make claims that Schering-Plough won't be able to, says Kurt Graves, Vertex's chief commercial officer. It also could strengthen the overall package of evidence supporting use of telaprevir, which is being tested in a pivotal study among patients new to treatment, called Advance.

There's much buzz in the medical and investment communities about both new drugs, protease inhibitors, which have been shown to be about twice as effective at curing the disease as the standard treatments.

Many patients can't stand to take the two drugs used in those standard treatments, pegylated interferon and ribavirin, because they cause flu-like side effects, need to be taken almost a year, and only offer a cure about one-third of the time.

“We're in a position to be first, our drug can be used for all hepatitis C treatment-failure patients, and we're likely to be used in a 24-week regimen, not a 48-week regimen,” Graves says. “We think we're in a good position.”

It's hard to say precisely how many more patients might be eligible to receive telaprevir if the Realize trial is a success. Among treatment-failure patients, an estimated 30 percent are non-responders to standard therapy, while the rest generate some sort of response that isn't good enough or doesn't last, Graves says.

Roche's contender is being co-developed with Brisbane, CA-based Intermune, and is called ITMN-191. It is still in the earlier stages of development, although Roche recently paid its partner a \$15 million milestone payment, and Roche has said it plans to move into the middle stage of clinical trials. Those companies have experimented with a once-daily or twice-daily dose that could be more convenient than either the Vertex or Schering-Plough drugs, which are made to be taken three times a day. Vertex is also looking to protect its flank there, by running a test called C208 to see if a twice-daily form of telaprevir can be shown equivalent to the regular form.

Wall Street will tune in next to the American Association for the Study of Liver Diseases meeting in November, where Vertex is expected to present more data on telaprevir trials in front of an audience of leading physicians. If the data look good, then Vertex shouldn't have much trouble enrolling patients in the Realize trial. It will still be at least a couple years before we know for sure whether today's strategy will pay off with greater market share in what's shaping up to be a feisty new pharmaceutical market.

Sep 10, 2008

Hepatitis C patients may have abnormal blood sugar

www.reuters.com

NEW YORK (Reuters Health) - Nearly two thirds of patients with chronic hepatitis C infection may have abnormal blood sugar levels, according to a report in the *American Journal of Gastroenterology*.

Blood sugar, or "glucose," abnormalities "are common and easily underestimated among patients with chronic hepatitis C infection," Dr. Ming-Lung Yu from Kaohsiung Medical University, Taiwan told Reuters Health. Careful evaluation for undetected glucose abnormalities is "essential" in caring for chronic hepatitis C patients.

Yu and colleagues compared the prevalence and characteristics of glucose abnormalities among 522 chronic hepatitis C patients and a comparison group of 447 without hepatitis C infection ("controls"), based on the results of an oral glucose tolerance test.

After excluding the subjects who were known to have diabetes, just over one third of the hepatitis C patients (34.2 percent) had normal results on the oral glucose tolerance test, the authors report, whereas 42.8 percent had impaired glucose tolerance and 23.0 percent had undiagnosed diabetes.

In contrast, 64.7 percent of the controls had normal levels of glucose, 32.4 percent had impaired glucose tolerance, and 2.9 percent had diabetes.

A family history of diabetes, male gender, advanced fibrosis stage of hepatitis, and increasing age each increased the risk of having glucose abnormalities, according to additional analyses.

Two consecutive fasting plasma glucose measurements or randomly measured glucose levels greater than 200 milligram per decaliter were not sufficient to confirm glucose abnormalities in the patients with chronic hepatitis C infection, Yu noted.

"Since family history, insulin resistance, age, and obesity are predisposing factors associated with diabetes in chronic hepatitis C patients, we would recommend an oral glucose tolerance test for chronic hepatitis C patients who are older than 40 years old," have a family history of diabetes or who are overweight, Yu advised.

Antioxidant shows promise for "chemo-brain"

www.reuters.com

By Amy Norton

NEW YORK (Reuters Health) - A new animal study suggests that antioxidant therapy may prevent the memory and attention problems that plague many cancer patients undergoing chemotherapy.

Often called "chemo-brain," such mental side effects are seen in up to 70 percent of chemotherapy patients by some estimates.

In the new study, researchers at West Virginia University School of Medicine in Morgantown looked at whether injections of a powerful antioxidant called N-acetyl cysteine, or NAC, could prevent chemo-related memory changes in rats.

The researchers first exposed one group of rats to two drugs commonly used to treat cancer, Adriamycin and Cytosan. They found that compared with a group of control animals, the chemo-exposed rats showed a decline in standard tests of rodent memory.

However, that mental fog was completely prevented when the researchers gave the rats NAC injections three times per week during chemotherapy administered four times per week.

The findings, published in the journal *Metabolic Brain Disease*, are promising. But it is far too soon for chemotherapy patients to turn to antioxidants for preventing chemo-brain, according to lead researcher Dr. Gregory W. Konat.

"I wouldn't suggest that patients do anything now," he told Reuters Health. More lab research is needed before NAC can even be moved into human clinical trials, let alone be given to patients, Konat said.

Chemotherapy patients should also not take large doses of other commonly available antioxidants, like vitamin C, according to the researcher.

Konat noted that a long-standing concern with antioxidants is that they could theoretically interfere with the effectiveness of chemotherapy.

Antioxidants protect cells by neutralizing cell-damaging substances called oxygen free radicals; it's thought that this damage, known as oxidative stress, may be what's responsible for the mental side effects of chemotherapy.

However, it's also thought that chemotherapy kills cancer cells, at least in part, by creating oxidative stress. So in theory, taking antioxidants could weaken the cancer-fighting ability of chemotherapy drugs.

A recent analysis of past studies suggests that antioxidants do not, in fact, diminish the effectiveness of chemotherapy, Konat said.

Still, he added, caution is in order. "We're dealing with a very serious condition here," he pointed out.

Given the unknowns, Konat advises chemotherapy patients to not self-treat with antioxidants or take any supplement without talking to their doctors first.

SOURCE: Metabolic Brain Disease, September

A potential approach to treatment of hepatitis B virus infection

<http://www.physorg.com>

Eukaryotic cells employ multiple strategies of checkpoint signaling and DNA repair mechanisms to monitor and repair damaged DNA. There are two branches in the checkpoint response pathway—ataxia telangiectasia-mutated (ATM) and ATM-Rad3-related (ATR). Many viruses are now known to interact with DNA damage sensing and repair machinery.

These viruses have evolved tactics to eliminate, circumvent, or exploit various aspects of the DNA damage response of the host cell. Strategies include the activation of repair proteins or the targeting of specific cellular factors for degradation or mislocalization. Exploiting the activation of the DNA damage pathway by viral replication for the generation of antiviral drugs needs to be examined.

In the human immunodeficiency virus (HIV), it has been clearly determined that the prevention of viral integration inhibits viral replication and promotes cellular apoptosis. Thus, the ATM-specific inhibitor ku55933 can inhibit HIV replication in primary T cells.

Despite the availability of a safe and efficient vaccine, chronic hepatitis B virus infection remains a major health problem worldwide. Interferon treatment is effective in only approximately one-third of the patients and produces considerable side effects. Long-term treatment with the second-generation nucleoside analogue lamivudine (lam) efficiently inhibits HBV replication with frequent viral polymerase mutations. We found that HBV infection triggered an ATR-dependent DNA damage response, resulting in increased ATR and Chk1 phosphorylation levels, however, ATR checkpoint signaling was blocked downstream of the p53-dependent pathway to evade apoptosis by p21 degradation. We have designed a strategy to select new drug targets that inhibit a cellular gene required for HBV replication or restore a response stalled by HBV in the ATR DNA damage pathway.

A research article to be published on August 28, 2008 in the *World Journal of Gastroenterology* addresses this question. The research team led by Professor, Zhong from Beijing Institute of Biotechnology used report that HBV infection activates and exploits the DNA damage response to replication stress. They investigated whether the inhibition of DNA damage response by CF, TP and UCN01 or the restoration of p21 expression by p21 transfection or proteasome inhibition would lead to suppressed HBV replication.

They set up a chronic HBV infection model by culturing hepatocyte HL7702 cells with HBV-positive serum without washing off input virus as conventional. HBV DNA titers inside the infected cells represent the final viral amount including the infected DNA without being degraded and the newly synthesized HBV DNA. In this way, studying the efficacy of DNA damage response inhibitors on HBV infection and replication was available. In addition, since DNA damage response is an acute response that happens quickly after virus infection, they assume that early intervention of DNA damage pathway will function more efficiently, thus can be used clinically as HBV infection therapy during its early infectious stage or fulminant HBV infection.

Source: *World Journal of Gastroenterology*

Sep 11, 2008

Evidence to support belief in transmission of hepatitis C by sharing drug sniffing equipment

www.aidsmap.com

Roger Pebody

Hepatitis C can be detected in the nasal passage, and in straws which are inserted in the nose, report researchers in the October 1st edition of *Clinical Infectious Diseases*. Their findings support the hypothesis that hepatitis C can be transmitted by sharing straws or banknotes which are used to snort drugs.

The theory of hepatitis C transmission through this route is that frequent or long-term sniffing or snorting of drugs such as cocaine can cause damage and bleeding in the nasal passage. Straws or banknotes that are inserted in the nose could come into contact with hepatitis C infected blood or mucus, which may then be transmitted to someone else sharing the same straw.

In recent years there have been numerous outbreaks of hepatitis C among HIV-positive gay men in Europe. Whilst there is a growing body of evidence that infection is associated with sexual practices including fisting, use of sex toys and group sex, some studies have also suggested that sniffing drugs may contribute to transmission.

At the same time, in many countries up to a quarter of hepatitis C infections remain unexplained, with individuals reporting no risky practices such as use of shared drug injection equipment.

And a number of epidemiological studies in largely HIV-negative populations (typically, blood donors or street drug users who do not inject) have found an association between snorting drugs and hepatitis C infection. Nonetheless not all studies have reported this finding, and there have been some criticisms of the methodological quality of these studies.

However, until now no study has examined the virological plausibility of the belief that sharing equipment to sniff drugs may contribute to hepatitis transmission. Investigators in New York therefore recruited 38 adults who snort drugs and have hepatitis C at a neighbourhood health clinic.

Tests conducted included:

- Nasal swabs to test for the presence of hepatitis C and blood in the nasal passage
- Each subject was asked to inhale air through plastic straws, which were then tested for hepatitis C and blood
- An examination of the nasal cavity to check for disease.

In these tests, hepatitis C RNA was detected using the same sort of technology as a viral load test.

A third of the sample was coinfecting with HIV, and 45% with hepatitis B. Hepatitis C viral load varied widely in the sample, with a mean of 5000 copies/ml. Liver function tests for ALT (alanine aminotransferase) indicated some damage, with a mean of 47 u/l.

The researchers were able to detect hepatitis C on 13% of the nasal swabs, and on 5% of the sniffing straws.

Blood was detected in the samples more frequently than hepatitis C. However whether blood was present or not did not predict whether hepatitis could be found. For example, of the five nasal swabs that were positive for hepatitis, there were no traces of blood on two of them.

Pathologies and damage to the nasal passage could increase the risk of hepatitis transmission. Among other problems, more than four out of ten subjects reported having a runny or stuffy nose at least once a week. Rates of inflammation of the nasal membrane were high at 71%, while rates of inflammation of the sinuses were normal.

It is known that hepatitis C can remain infectious outside the body for up to 16 hours. However the authors acknowledge that little is known about the quantity of virus needed for transmission. They suggest that when drugs are being snorted, there is greater discharge of nasal fluids and blood, and the quantity of virus is likely to be larger.

The authors believe that their most significant finding is that hepatitis C can be transferred onto sniffing implements. Nonetheless they recommend further studies to confirm this mode of transmission and its contribution to the spread of hepatitis C.

Reference

Aaron S et al. Intranasal transmission of hepatitis C virus: virological and clinical evidence. *Clinical Infectious Diseases* 47: 931-934, 2008.

New Lawsuit Filed in Hep C Case

<http://www.lasvegasnow.com>

Edward Lawrence, Reporter

A new lawsuit has been filed in the hepatitis C scare. This time, the case is not about the doctors involved in the scare. Now lawyers are going after the patient's own insurance company.

Alyne Griffiths says she was forced to go to the Endoscopy Center of Southern Nevada. Her insurance company would only cover her two procedures if she went to a doctor at that center. She says going there gave her hepatitis C.

Griffiths looks and acts like a typical grandmother. Now 71-years-old, she retired from her art store business in early 2005 and moved to Las Vegas from Sacramento.

"California is really expensive and my daughter lives in Las Vegas, so I came to Las Vegas," she said.

She had two procedures at the Endoscopy Center of Southern Nevada -- one in 2005 and another in 2006. After that, everything changed, "I am used to being a real active person. I like to garden and do physical things. I go out now. I go out and in a few minutes, I got to go back in and sit down for a while."

Griffiths had no idea why she felt tired until March of 2008 when the health district sent out a letter to 63,000 people saying they may have been exposed to hepatitis C at two endoscopy centers. Griffiths tested positive.

"This should be the best time of my life -- retired and do what I want, when I want it. Now all of the energy is gone," she said.

She says not only would PacifiCare of Nevada only cover the procedures at the endoscopy center, for hepatitis C treatment, the insurance company will now only refer her to the very doctor who performed the procedures who she says gave her hepatitis C.

"I am not going to go back to him. Because why would I?" she said.

"They are sending her back to providers who were providing services at that clinic at the time all of this came down," said Attorney Gerald Gillock. He filed the lawsuit on behalf of Griffiths.

He says the insurance company had a responsibility to look out for the benefit of the patient. He thinks they failed miserably with Griffiths.

The lawsuit was filed Wednesday morning, but a hearing date has not yet been set. Lawyers tried to sue the insurance company of the doctors who own the endoscopy center. A judge threw that out saying the company did not have the obligation of inspecting the doctor's office.

AIDS, Hep C Activists Protest Governor's Funding Cuts

<http://www.nyl.com>

By: NY1 News

Dozens of people living with HIV/AIDS and hepatitis C rallied outside the governor's Manhattan office Wednesday, to protest what they say is a lack of funding and treatment.

After Governor David Paterson referred to state legislators as "bloodsuckers" this week, activists created a mock graveyard, saying the governor is the one inflicting harm on the public health system.

They want the governor to increase state investment in AIDS and hepatitis C programs.

"This is his community that's dying out here. Come out here, acknowledge us, do something," said a protester. "Our people are dying. How is it that you can turn a deaf ear to all that's going on?"

NY1 reached out to the governor's office for comment, but received no response Wednesday.

Natalie Cole: 'My Life Crumbled Before My Eyes'

<http://www.people.com>

By Marisa Laudadio

After revealing in July that she has hepatitis C, Grammy winner Natalie Cole is opening up about the agonizing treatment she's getting for the liver disease.

"I give myself a weekly injection of chemotherapy in my thigh," Cole, 58, tells PEOPLE in its new issue. "When I started in May, I thought I was dying. I couldn't get out of bed for three weeks – literally. I was nauseous every day. I lost 15 pounds from not eating."

Doctors diagnosed the disease in April after a routine blood test. They say Cole likely contracted hepatitis C – which remained dormant in her body for 25 years – from sharing dirty needles when she was a heroin addict in the early '80s. "My life crumbled before my eyes," she tells PEOPLE.

"I've learned a lot of lessons," Cole adds. "Yes, I could have handled some things better. But they've also made me who I am today."

Although she is still undergoing chemo until the end of the year to improve her chances of being cured, Cole's doctor confirms she is already virus negative after more than three months of treatments.

Cole says her "the show must go on" philosophy has helped her cope with her health issues. Her new album of pop standards, *Still Unforgettable* was released on Sept. 9, and she is planning an October tour.

The new album, a sequel to her 1991 Grammy-winning CD *Unforgettable ... With Love*, features a new duet with her late father Nat King Cole called "Walkin' My Baby Back Home."

"I've worked so hard on this record – it's the first one I produced – I couldn't see pushing it back [while I went through my treatment]," says Cole. "So we're going to barrel through and kick butt. And if I have to, I'll kick butt sitting down."

Other celebrities who have publicly battled the disease – which affects about 200 million people worldwide, including 4 million in the U.S. – include Pamela Anderson, David Crosby and Naomi Judd.

Cole says Judd has been a source of support since her diagnosis. "Sometimes she leaves me little messages. You'd be surprised how that support goes a long way," says Cole.

Sep 12, 2008

Ask the Experts: Do cccDNA Levels Have a Role in Predicting Response to Treatment in Hepatitis B?

www.medscape.com

Paul Martin, MD, FACP; Hui Hui Tan, MBS, MRCP (UK)

Covalently closed circular DNA (cccDNA) is a crucial intermediate in the replication of the hepatitis B virus (HBV). In the host nucleoplasm, it acts as a template for continued virion production in chronically infected patients. Viral transcripts are transported from the nucleus into the cytoplasm, where they are translated into the various HBV proteins. Pregenomic RNA is then encapsidated and reverse-transcribed into new partially double-stranded viral genomes. cccDNA remains in the nucleus as long as the infected hepatocyte survives, maintaining a viral 'pool' in chronic infection. Because cccDNA does not circulate in the blood, measurement of its levels requires hepatic tissue (cccDNA is quantified by polymerase chain reaction [PCR] assay),[1] whereas serum hepatitis B surface antigen concentration provides an indirect assessment of its concentration in the hepatocyte.[2]

It is unclear whether currently approved treatments for HBV infection are able to eliminate cccDNA in the absence of hepatocyte lysis. Return of HBV replication after apparently successful treatment with suppression of viral replication, is attributed to remnant intrahepatic cccDNA. Recent studies have attempted to correlate cccDNA levels with treatment outcomes. To date, human studies have been small (n < 80), although results appear promising. Most studies have found pre-treatment cccDNA load or intrahepatic total HBV viral load (quantified with PCR) to be inversely proportional to hepatitis B e antigen (HBeAg) clearance rates and to sustained virologic response rates. A German study of 26 HBeAg-positive patients treated with 48 weeks of combination pegylated interferon alfa-2b and adefovir reported a correlation between cccDNA reduction during the treatment period and treatment response.[3] Another study of 47 Chinese patients found that log cccDNA levels were significantly lower among subjects who achieved durable virologic responses (defined as durable HBeAg seroconversion plus serum HBV DNA < 500,000 copies/mL from end-of-treatment until week 52 after treatment) and concluded that both cccDNA and intrahepatic total HBV DNA levels at end of therapy (with combination pegylated interferon and lamivudine or lamivudine monotherapy) were superior to serum HBV DNA as surrogates of virologic response.[4]

There are no human data correlating cccDNA levels with prediction of treatment response to the newer nucleos[t]ide analogues yet. There has been no correlation reported between cccDNA levels and treatment response in HBeAg-negative chronic HBV patients yet either. Although current data on the use of cccDNA to predict treatment response in HBV infection are limited, the initial results appear promising and it is likely that baseline levels or degree of reduction during treatment do predict treatment response. However, larger studies will be needed before

cccDNA levels can be validated and recommended as a tool to assess or predict response to treatment in hepatitis B.

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