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LIVER UPDATE

VOL. 6, NO. 2 / SPRING 2005

A PUBLICATION OF THE CENTER FOR LIVER DISEASES AND THE INOVA TRANSPLANT CENTER

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Save the Date: April 7, 2006

- **Creating the Next Revolution in Molecular Medicine: The Application of Translational Research in Clinical Medicine**

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  Details TBA

Inova Health System is a not-for-profit health care system based in Northern Virginia that consists of hospitals and other health services including emergency and urgent care centers, home care, nursing homes, mental health and blood donor services, and wellness classes. Governed by a voluntary board of community members, Inova's mission is to improve the health of the diverse community we serve through excellence in patient care, education and research.

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LIVER UPDATE

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New Drug Therapy for Hepatitis C

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INTRODUCTION

Chronic hepatitis C virus (HCV) infection affects a large number of patients worldwide. While our current therapies are effective in approximately 50 percent of patients, treatment is costly, prolonged, associated with significant side effects, and is not suitable for certain groups of patients. For these reasons, improved treatment regimens are necessary. Several new treatment options are discussed in this article.

MODIFICATIONS TO THE CURRENT INTERFERON REGIMEN

Challenges still exist with respect to interferon (IFN) treatment. Several groups have thus attempted to modify naturally occurring IFNs. These modifications include alteration of the primary amino acid sequences, the addition of polyethylene glycol, alterations of glycosylation patterns and the production of fusion proteins. The addition of polyethylene glycol to therapeutic IFN alfa proteins has been shown to increase plasma exposure and led to increased response rates. A fusion protein of IFN alfa-2 and human serum albumin, Albuferon, has entered clinical trials for the treatment of chronic hepatitis C.

Oral IFN inducers represent another class of compounds that may generate an effective immune response by induction/modulation of cytokine responses. The central challenge in the use of such agents is delivery of effective doses to the liver. Alternatively, low molecular weight molecules may offer similarly useful immune-modulating properties. The development of imidazoquinolones and other nucleoside analogs such as ANA245 are examples of these agents.

RIBAVIRIN-LIKE MOLECULES

Ribavirin monotherapy is ineffective in inducing sustained viral clearance, but it significantly enhances the sustained viral clearance rate when combined with IFN. There are four proposed mechanisms by which ribavirin enhances IFN efficacy, including:

- immune-mediated activity on the host Th1/Th2 balance
- inhibition of host enzyme inosine monophosphate dehydrogenase (IMPDH) activity
- weak inhibitory activity against the RNA dependent RNA polymerase (RdRp)
- induction of RNA mutagenesis.

Hemolytic anemia is a frequent side effect that limits ribavirin dosing, emphasizing the need for alternative molecules with similar mechanisms and efficacy and less toxicity.

Viramidine is a prodrug which can be converted to ribavirin by adenosine deaminase. As the liver is rich in deaminases, viramidine is converted to ribavirin and its phosphorylated metabolites and is preferentially retained in the liver. In phase I studies, viramidine showed similar adverse event profile as ribavirin. However, the hemoglobin drop with the highest dose was lower than the hemoglobin drop with conventional combination therapy. A phase II proof-of-concept study in combination with pegylated IFN alpha

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Continuing Medical Education

Liver Diseases, Liver Cancer and Liver Transplantation

Saturday, Sept. 24, 2005
7:30 a.m. - 12:30 p.m.

Inova Fairfax Hospital
Physicians Conference Center

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www.inova.org/inovapublic.srt/liver/index.jsp
(scroll down to Continuing Medical Education)

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HEPATITIS C, from page 1

is ongoing. IMPDH inhibitors, such as mycophenolic acid (Cellcept) and VX-497, are also currently being studied in patients with chronic hepatitis C, but preliminary results showed minimal direct anti-viral efficacy, similar to ribavirin.

Several immunomodulatory drugs are currently being used in combination with IFN or pegylated IFN in clinical trials. Thymosin alfa-1 promotes T-cell maturation and natural killer (NK) cells and differentiation of pluripotent stem cells. The drug is currently being evaluated in large phase II/III trials in combination with pegylated IFN alfa. IL-10, an anti-inflammatory drug, failed to show any beneficial histologic and anti-fibrotic effects in a randomized controlled trial, whereas a phase II study of IL-12, a different pro-inflammatory drug, suggested a lack of efficacy and significant toxicity.

NUCLEIC ACID-BASED THERAPY: ANTISENSE OLIGONUCLEOTIDES, RIBOZYMES AND siRNAS

The aim of the antisense approach is to exploit the high affinity and selectivity of nucleic acid hybridization for the development of highly specific drugs. Viral genomes contain numerous unique nucleic acid sequences not present in the human genome that have the potential to act as a virus-specific antisense target. Several drugs, including ISIS 14803, have been identified as antisense oligonucleotides that inhibit the translation of HCV RNA. Two clinical studies of ISIS 14803 monotherapy have shown reductions in plasma HCV RNA levels in 30 percent of patients. Transient asymptomatic alanine aminotransferase (ALT) flares, up to 30 times, were also observed in some patients.

Ribozymes, another nucleic acid-based strategy, are catalytic RNA molecules that cleave specific RNA sequences. They contain a catalytic core region flanked by binding arms with specific nucleotide sequences determined by the complementary base sequence of the target RNA. Heptazyme™ is a synthetic ribozyme that is chemically modified for resistance to enzymatic and chemical degradation. Preclinical results indicated that this drug significantly inhibits viral replication in cell culture . Phase II results indicated that Heptazyme as monotherapy led to a reduction in serum HCV RNA levels in 10 percent of patients but the development of Heptazyme has been halted for toxicity reasons.

A related and new potential class of therapeutics makes use of RNA interference (RNAi), a recently discovered process where cells down-regulate gene expression through destruction of a specifically targeted mRNA. The RNAi process is mediated inside the cell by a naturally occurring protein. Rational design of double-stranded RNA permits the down-regulation of virtually any gene. In human cells, these double-stranded RNAs, known as silencing RNAs (siRNAs), show biological activity as short fragments of 20-23 residues. Stabilized siRNA compounds are currently being evaluated in the preclinical setting for their potential activity against HCV.

HCV PROTEASE INHIBITORS

The search for protease inhibitors has been hampered by the hydrophobic nature of the protein and by the autocatalytic nature of the cleavage.

Recent research has led to the discovery of BILN 2061, a small, selective and potent inhibitor of the NS3 serine protease. BILN 2061 was administered for 48 hours in HCV-infected patients in early clinical development studies. Administration resulted in a rapid, dose-dependent HCV RNA decrease up to four logs within two days at the highest doses, with a progressive return to baseline levels within a week after treatment withdrawal. BILN 2061's further testing has been halted due to some potential toxicity.

HCV NS3 HELICASE INHIBITORS

A few small-molecule inhibitors of the NS3 helicase with activity in vitro have been reported, but their inhibitory mechanisms, specificity and potential efficacy in the clinical setting remain unclear.

HCV RDRP INHIBITORS

One category of inhibitors of viral polymerases is nucleoside (substrate) analogues (cyclic or acyclic). Inhibitors of the HCV RdRp have been identified through the use of high throughput screening. Several of these compounds have encouraging preclinical profiles. Preliminary *in vitro* results suggest that resistance to RdRp inhibitors may occur in the clinical setting.

A few orally bio-available inhibitors of the HCV RdRP are under study in early clinical trials, such as JTK-003 and JTK-109, and NM283. The efficacy of NM283 against HCV genotype 1 was established in a one week study in chronically infected chimpanzees. Median drops in HCV viral load of -0.83 and -1.05 log10 were observed. NM283 has recently entered early phase clinical trials.

ANTIFIBROTIC APPROACHES

The liver offers a unique advantage as a target for orally administrated antifibrotic agents, since those with efficient hepatic first-pass extraction will have inherent liver targeting by minimizing systemic distribution and non-liver adverse effects. New anti-fibrotic therapies may be derived from at least three sources: (i) existing drugs with established safety profiles which may gain an additional indication for use in hepatic fibrosis (for example: IFN alfa, angiotensin conversion enzyme inhibitors, TNF alfa antagonists, antioxidants, IFN gamma, etc); (ii) drugs under development for other diseases that may have additional value in hepatic fibrosis; and (iii) agents specifically developed for use in liver

fibrosis. However, unlike direct antiviral drugs, the efficacy of these drugs cannot be simply assessed in short-term clinical trials, and a clinical benefit may only be apparent after a prolonged period of treatment.

CONCLUSION

The research environment and new drug development for patients with hepatitis C is exciting. A large number of new HCV drugs are currently in the pipeline, with several of them having already reached the clinical phase of development. It is clear that only a few of these candidates will be approved for clinical use in the treatment of HCV infection. It is however encouraging to foresee multiple therapies with complementary targets that could lead to cure of HCV infection in a greater proportion of patients.

George Mason University and Inova Health System Announce New Translational Research Centers

George Mason University and Inova Health System have partnered to create the George Mason - Inova Health System Translational Research Centers; a joint initiative to implement proteomics and genomics research in cancer, metabolic syndrome, and liver diseases.

The centers will be co-directed by Zobair Younossi, MD, MPH (director of Inova Fairfax Hospital's Center for Liver Diseases) and Vikas Chandhoke, PhD (George Mason University's associate dean of research). In addition, the collaboration has recruited internationally renowned scientists Lance A. Liotta, MD, PhD, from NCI and Emanuel F. Petricoin III, PhD, from the FDA. To learn more about this center, please call Dr. Younossi or Scarlett Magee at **703-208-6650**.

Faculty Presentations at Meetings

Dr. Younossi was faculty for the following meetings:

- Obesity-Related Non-Alcoholic Fatty Liver Disease. Thomas Jefferson University, GI Grand Round 2005.
- Non-Alcoholic Steatohepatitis. Washington VA Hospital, Gastroenterology Conference, 2005.
- Management of Non-Alcoholic Fatty Liver Diseases. Walter Reed and American College of Gastroenterology Bi-annual GI Course, McLean, VA 2005.
- Fatty Liver in Obesity: What We Know and Don't Know? Digestive Disease Week, Chicago, IL. May 2005.
- The Impact of Cirrhosis and Liver Transplantation on Quality of Life. American Transplant Congress Meeting, Seattle, WA. May 2005.

Publications

- S Saab, A Ibrahim, A Shpaner, Z Younossi, C Lee, F Durazo, S Han, K Esrason, V Wu, D Farmer, M Ghobrial, C Holt, Pharm, H Yersiz, L Goldstein, M Tong M, R Busuttil. Meld Fails to Measure Quality of Life in Liver Transplant Candidates. Liver Transplantation and Surgery, 2005 Feb; 11(2):218-23.
- B Spiegel, ZM. Younossi, RD Hayes, D Revicki, S Robbins, F Kanwal, The Impact of Hepatitis C on Health Related Quality of Life: A Systematic Review and Quantitative Assessement. Hepatology. 2005 Apr; 41(4):790-800.
- J Ong, H Elariny, R Collantes, A Younoszai, V Chandhoke, HD Reines, Z Goodman, ZM Younossi. Predictors of Nonalcoholic Steatohepatitis and Advanced Fibrosis in Obese Patients Obesity Surgery 15(3):310-5. 2005.
- S Srivastava, Z Younossi. Can Lamivudine Prevent the Progression of Liver Disease in Chronic Hepatitis. Evidence-Based Gastroenterology. 6(1):26-27, March 2005.
- J Ong, R Collantes, A Pitts, L Martin, M Sheridan, Z Younossi. High Rates of Uninsured Among Hepatitis C Positive Patients. Journal of Clinical Gastroenterology. (In Press 2005)
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- A Baranova, K Schlauch, S Gowder, R Collantes, V Chandhoke, Z Younossi. Microarray Gene Expression Studies of Obesity-Related Non-Alcoholic Fatty Liver Disease. Liver International. (In Press 2005).

Research Presentations

- G-H Wang, A Mehrotra, JP Ong, ZM Younossi, Z Goodman. P62 as a Reliable Marker for Mallory Bodies in Non-Alcoholic Steatohepatitis (NASH). United States and Canadian Academy of Pathology Annual Meeting, Washington DC, 2005.
- J Estep, G Grant, L O' Reilly, J Piper, J Jonsson, M Gupta, JP Ong, V Chandhoke, ZM Younossi. Expression Of Genes Associated With Apoptosis Of The Hepatic Stellate Cells Obtained From The Explanted Livers. American Transplant Congress/American Society of Transplantation, Seattle, WA. 2005
- D Farmer, R Collantes, S Makay, JP Ong, H Gujral, L Farquhar, ML Carniello, R Sjogren, ZM Younossi. Filgrastim for the Neutropenia Associated with Combination Therapy in Chronic Hepatitis C (Submitted). Digestive Disease Week 2005.
- A Baranova, R Collantes, K Schlauch, H Elariny, S Gowder, A Afendy, J Ong, Z Goodman, Vi Chandhoke, Z Younossi. Adiponectin Gene Expression In The Intra-Abdominal Adipose Tissue Of Patients With Non-Alcoholic Fatty Liver Disease (Nafld): Diabetics Vs. Non-Diabetics (Submitted). Digestive Disease Week 2005

Current Clinical Trials

- Clinical Research Protocols for Patients with Non-Alcoholic Fatty Liver Disease and Obesity
- Clinical Research Protocols for Hepatitis C
- Clinical Research Protocols for Hepatitis B