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LIVER UPDATE

VOL. 6, NO. 1 / WINTER 2005

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

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Save the Date

- **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
  This lecture series will serve to update physicians and others in the health care field on new information related to chronic liver diseases and liver transplantation.

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 provide quality care and improve the health of the diverse communities we serve.

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Update on Chronic Hepatitis B

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Chronic hepatitis B virus (HBV) infection is a leading cause of cirrhosis and hepatocellular carcinoma (HCC) in the world. Endemic areas include Asia, Africa, the Middle East and Alaska. It is estimated that 350 million individuals worldwide and 1.25 million in the United States are chronically infected with HBV.

Those who test positive for HBsAg for at least six months are considered chronically infected with HBV. To assist in the management of chronic HBV, diagnostic criteria have been proposed. (See Table) HBsAg carriers with normal liver enzymes and low level of virus generally have mild disease and do not require treatment. They may still be at some risk for development of HCC and screening for HCC should be considered, especially in those who have a family history of HCC.

Those persons with elevated liver enzymes and high levels of viral replication usually have chronic hepatitis and are at risk for progressive liver disease. HBeAg-positive chronic hepatitis B patients have detectable HBeAg and believed to have the so-called "wild-type" of HBV. Patients with chronic hepatitis B and viremia, but without HBeAg, have the so-called "precore mutant" type of HBV. These patients may have spontaneous flares and remission with significant histologic disease. Both HBeAg-positive and HBeAg-negative chronic HBV persons are candidates for antiviral therapy.

Viral nucleic acid testing in blood has become increasingly important for the management of chronic hepatitis B, in particular in the follow-up of patients on antiviral therapy and in the surveillance for the development of viral mutants on therapy. There are several commercially available assays for HBV-DNA that have varying limits of sensitivity ranging from 10^2 for the polymerase chain reaction (PCR) based assays to 10^5 copies/ml and different ranges of linearity.

Recently, there has been an increase in interest in HBV genotypes and their association with liver disease severity and treatment response. HBV has been classified into eight genotypes (genotypes A to H). The genotypes have a variable worldwide distribution. In the United States, all the genotypes are represented, with genotypes A and C being the most common. Preliminary information suggest that genotype B is associated with less severe liver disease than genotype C, and genotype A and B may be associated with better response rates to interferon alfa therapy compared to genotypes C and D. These findings need confirmation in larger studies.

TREATMENT OF HEPATITIS B

The treatment of Chronic Hepatitis B has for its goal, the prevention of progression of liver disease by sustained suppression of viral replication. Evidence from many studies has shown that patients who have active replication and who have evidence of liver disease on biopsy are more likely to develop progressive liver disease. Therefore, treatment is generally recommended for the patient with (1) persistently abnormal serum aminotranferases who has (2) active viral replication based on the presence of HBV-DNA and (3) if available, evidence of chronic hepatitis on liver biopsy.

At the present time, treatment of inactive carriers is not recommended and that of patients with normal serum aminotransferases is controversial.

Currently, there are three approved medications for the treatment of chronic hepatitis B – interferon-alfa, lamivudine, and more recently, adefovir dipivoxil. Interferon-alfa has been approved for treatment of chronic hepatitis B with the usual regimen consisting of five million units every day or 10 million units three times a week, given subcutaneously for 16 weeks in HBeAg-positive patients and 12 months for HBeAg-negative patients. Interferon-alfa has both antiviral and immunomodulatory activity and has

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been found in a meta-analysis of 15 randomized, controlled trials in HBeAg-positive chronic hepatitis B to result in HBeAg loss in about one third of the patients. Long-term follow-up of patients who achieved HBeAg seroconversion showed improvement in survival compared to patients who did not achieve seroconversion. HBeAg seroconversion with interferon-alfa may be accompanied by a transient rise in serum aminotransferases right before losing HBeAg.

Factors that have been shown to predict a favorable response to interferon-alfa include low HBV-DNA levels, high serum aminotransferases, and evidence of active liver disease on liver biopsy. In patients with HBeAg-negative chronic hepatitis B, the efficacy of interferon-alfa is determined more by having a sustained loss of HBV-DNA accompanied by persistently normal serum aminotransferases. Response rates of up to 40 to 60 percent have been shown, but relapse after discontinuation of therapy is high, resulting in a sustained response rate of only about 15 to 25 percent. That is slightly lower than the response rates seen in patients who are HBeAg positive.

Recently, peginterferon-alfa 2a alone given over a year was shown to lead to higher rates of sustained viral suppression in HBeAg-negative patients when compared to lamivudine alone. The addition of lamivudine to peginterferon-alfa 2a did not improve response rates. More importantly, HBsAg seroconversion was observed only in those who received peginterferon-alfa 2a and not in those who received lamivudine alone. Preliminary data in HBeAg-positive patients showed higher rates of HBeAg seroconversion in those who received peginterferon-alfa alone or in combination with lamivudine compared to lamivudine alone. Additionally, as in the HBeAg-negative patients, HBsAg seroconversion was observed only in those who received peginterferon-alfa 2a and not in those who received lamivudine alone.

The main drawback of interferon-alfa therapy is the adverse side effects that may become intolerable in some patients. Because interferon-alfa can cause immunologic clearance of HBV-infected hepatocytes, patients with advanced liver disease and cirrhosis can decompensate with this form of treatment. Therefore, patients with decompensated liver disease or those at risk for decompensation should not be treated with interferon-alfa.

Lamivudine is a nucleoside analogue that inhibits HBV replication. Several large randomized clinical trials have shown that HBeAg seroconversion occurred in up to 18 percent of patients at the end of one year of treatment. Durability of response among those who achieved HBeAg seroconversion can be seen in close to 80 percent of patients in some studies. Discontinuation of lamivudine treatment in patients who do not achieve HBeAg seroconversion generally results in relapse with reappearance of HBV-DNA in serum.

In patients with HBeAg-negative chronic hepatitis B, lamivudine has also been shown to be highly effective in suppressing viral replication which is accompanied by improvements in liver histology. However, relapse is very high after discontinuation of treatment. Extended use of lamivudine has been employed to address the issue of relapse after discontinuation of therapy. This strategy has been associated with the emergence of resistant strains of hepatitis B virus and recurrence of liver disease at rates of up to 14 percent at one year, 38 percent at two years, and 66 percent at three years. In a recently published study, the use of lamivudine was shown to delay disease progression in patients with advanced liver disease, underscoring the importance of identifying those patients with advanced liver disease for consideration for antiviral therapy.

Adefovir dipivoxil was also approved for the treatment of chronic hepatitis B. Adefovir dipivoxil is a nucleotide analogue that inhibits HBV replication. It is effective not only in suppressing wild type HBV but also in suppressing lamivudine-resistant HBV. After one year of treatment in HBeAg-positive patients, HBeAg seroconversion was noted in 12 percent of patients. With prolonged treatment, higher rates of

Diagnostic criteria for chronic HBV*

Inactive HBsAg carrier
- HBeAg negative, anti-HBe positive
- serum HBV-DNA < 10^5 copies/ml
- persistently normal ALT/AST levels
- liver biopsy showing no significant hepatitis (not routinely recommended)

HBeAg-positive chronic hepatitis B
- HBeAg positive, anti-HBe negative
- serum HBV-DNA > 10^5 copies/ml
- persistent or intermittent elevation in ALT/AST levels
- liver biopsy showing chronic hepatitis (optional)

HBeAg-negative chronic hepatitis B
- HBeAg negative, anti-HBe positive
- serum HBV-DNA > 10^4 copies/ml**
- persistent or intermittent elevation in ALT/AST levels
- liver biopsy showing chronic hepatitis (optional)

* by definition, HBsAg is positive for at least six months

** HBeAg-negative chronic hepatitis B can have fluctuating levels of HBV-DNA and may have significant liver disease at lower levels of HBV-DNA

HBeAg seroconversion have been reported. In HBeAg-negative patients, adefovir dipivoxil led to viral suppression and biochemical improvement in nearly half of the patients at one year. One distinct advantage of adefovir dipivoxil over lamivudine is the lack of viral resistance after one year of treatment. Viral resistance rates at two and three years of treatment are low at 2.0 and 3.9 percent, respectively.

SPECIAL POPULATIONS

In patients with HBV who receive immunosuppressive therapy or cytotoxic chemotherapy, reactivation or acute flares of hepatitis B can occur, potentially leading to liver failure. Several studies have shown that the administration of anti-HBV treatment such as lamivudine reduces the incidence and severity of such events. Antiviral prophylaxis is currently recommended in patients with chronic HBV who receive immunosuppressive therapy or cytotoxic therapy. Antiviral therapy is given at the onset of therapy and maintained for six months after completion of chemotherapy or immunosuppressive therapy.

Additionally, consideration should be given to test those persons who are at high risk for HBV infection for HBsAg prior to initiation of chemo-therapy or immunosuppressive therapy.

FUTURE TREATMENT

There are other antiviral agents that are undergoing active clinical testing, including entecavir, emtricitabine and clevudine, among others. In trials comparing entecavir to lamivudine, entecavir resulted in significantly greater viral suppression at 48 weeks in both HBeAg-positive and HBeAg-negative patients. Data on regimens containing two nucleoside analogues are eagerly awaited. Preliminary data shows that the combination of emtricitabine and adefovir dipivoxil showed greater antiviral activity than adefovir dipivoxil alone.

Faculty Presentations at International Meetings

Dr. Younossi was faculty for the following meetings:

- Non-Alcoholic Fatty Liver Disease: Management. American Association for Study of Liver Diseases. Post Graduate Course. Boston, MA. 2004.
- Non-Alcoholic Fatty Liver Disease: What to Do with Your Fatty Liver Patients. American College of Gastroenterology. Orlando, FL. 2004.
- Interaction between NAFLD and Hepatitis C. Asian Pacific Association for the Study of the Liver. New Delhi, India. 2004.
- Insulin Resistance and NAFLD. Asian Pacific Association for the Study of the Liver. New Delhi, India. 2004.
- Adherence and Side Effect Management During Antiviral Therapy for Hepatitis C. Indian Association for the Study of Liver Disease. New Delhi, India. 2004.

Publications

- S Herten, J Stoller, Z Younossi. Alpha-1 Antitrypsin Deficiency. (Book Chapter). Hepatology: A Practical Approach, First Edition. Elsievier Sciences. 2004.
- G Grant, Z Younossi. Association of NASH with Other Specific Disorders. Fatty Liver Diseases: Non-Alcoholic Steatohepatitis and Related Disorders, Book Chapter, First edition. Blackwell Publishers. 2004.
- Z Younossi, A McCullough, J Ong, D Barnes, A Post, A Tavill, D Bringman, L Martin, J Assmann, T Gramlich, K Mullen, R O'Shea, W Carey, R Ferguson. Obesity and Non-Alcoholic Fatty Liver Disease in Chronic Hepatitis C. Journal of Clinical Gastroenterology, Vol. 38:705-709, 2004.
- R Collantes, J Ong, Z Younossi. Non-Alcoholic Fatty Liver and the Epidemic of Obesity. Cleveland Clinic Journal of Medicine, Vol. 71(No.8):657-664; 2004
- J. Koff, Z Younossi. Hepatitis C with Normal Liver Enzymes: To Treat or Not to Treat. American Journal of Gastroenterology, Vol.9:6;972, 2004.
- B Mullhall, Z Younossi. Non-Alcoholic Steatohepatitis. Current Treatment Options in Gastroenterology, 7:423-430, 2004
- S Sarbah, T Gramlich, A Younoszai, M. Goormastic, A Dibisceglie, J Cooper, R Seneca, Z Younossi. Risk Factors for Hepatocellular Carcinoma in Patients with Cirrhosis. Digestive Disease and Sciences, 49(5):850-853, 2004.
- Younossi Z. Interactions between Nonalcoholic Fatty Liver Disease (NAFLD) and Hepatitis C Viral Infection. Journal of Gastroenterology and Hepatology 19, S253-S257; 2004.
- Younossi Z. Effective Hematologic Side Effect Management in Treatment of Chronic Hepatitis C. Clinician's Companion VII 2004.
- T Gildea, WC. Cook, DR. Nelson, A Aggarwal, W Carey, ZM. Younossi, AC. Arroliga. Predictors of Long-term Mortality in Patients with Cirrhosis of the Liver Admitted to a Medical ICU. Chest 126(5):1598-603; 2004.
- T Taddei, ZM Younossi, The Efficacy of Weight Reduction In Nonalcoholic Fatty Liver Disease. Evidence Based Gastroenterology 2004.
- P Pockros, M Shiffman, E Schiff, M. Sulkowski, ZM Younossi, DT. Dieterich, T Wright, SH. Mody, K Tang, BL. Goon, PJ. Bowers, G Leitz, N Afdhal and the PROACTIVE Study GroupEpoetin alfa Improves Quality of Life in Anemic HCV-infected Patients Receiving Combination Therapy. Hepatology 40(6):1450-8, 2004.
- B Mullhall, Z Younossi. The Impact of Adherence on Outcome of Antiviral Therapy of Chronic Hepatitis C. Journal of Clinical Gastroenterology 39:S23-S27, 2005.
- R Collantes, Z Younossi. Management of Hematologic Side Effects of Peginterferon and Ribavirin with Growth Factors. Journal of Clinical Gastroenterology 39(1):S9-S13, 2005.

Current Clinical Trials

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