Liver Update

A publication of the Center for Liver Diseases and the Inova Transplant Center

Treatment Options For Chronic Hepatitis C

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Hepatitis C (HCV) remains one of the most common causes of chronic liver disease worldwide. An estimated 175 million people worldwide carry the antibody against this virus. Although chronicity is common (75-80 percent), only 20-25 percent develop cirrhosis. This rate of progression to cirrhosis is variable and can be affected by several factors, i.e. excessive alcohol consumption, age of acquisition, male gender and other currently unknown factors. In the setting of this tremendous disease burden and the potential for progression, HCV is currently the most common indication for orthotopic liver transplantation. Additionally, it is estimated that 8,000 to 10,000 individuals die from advanced liver disease related to HCV each year.

TREATMENT OF HEPATITIS C

Interferon-alfa (IFN-α) remains the backbone of therapy against HCV. These regimens have been associated with normalization of serum transaminases (biochemical response), clearance of HCV RNA from the serum (virologic response) and improvement in the liver histology (histologic response). The primary goal of anti-viral therapy is to achieve undetectable HCV RNA sustained for six months after discontinuation of treatment (sustained virologic response; SVR). In those achieving SVR, improvements in histology, biochemistry and health-related quality of life have been documented. Although HCV genotypes 1 and 4 have consistently been difficult to eradicate with antiviral therapy, other factors such as level of viremia, presence of histologic cirrhosis, obesity, etc. may also affect this response.

Meta-analysis and a number of additional studies evaluating standard IFN-α monotherapy for chronic HCV (three million units thrice weekly for 12 months) revealed an overall biochemical response of 40-45 percent with a sustained virologic response of 10-15 percent. Higher dose and longer duration of therapy add little to this sustained response.

Given this low rate of response to IFN-α monotherapy, combination regimens of IFN-α with other agents have been used. Although a number of agents have been investigated, a combination of IFN-α and ribavirin (a nucleoside analogue) has improved this efficacy. In one large multi-center clinical trial, sustained virologic response of 31 percent with 24 weeks and 38 percent with 48 weeks of combination therapy, versus six percent with 24 and 13 percent with 48 weeks of IFN-α monotherapy were reported.

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Re-treatment of the so-called "non-responders" with this combination results in 5-20 percent SVR.

The main disadvantage of standard IFN is its short half-life associated in high peaks and low troughs resulting from the every other day injections. It has been proposed that the low trough levels of IFN-α between the doses are associated with the development of "escape mutants" of HCV, which may be resistant to IFN-α, providing some basis for treatment failures. Attachment of polyethylene glycol (PEG) to the standard IFN-α will increase sustained blood levels, allowing for the convenience of once-weekly dosing and enhancing therapeutic efficacy of these interferons. As the PEG size increases, half-life will also increase and clearance by the kidneys may decrease.

Currently, there are two approved pegylated formulations of IFN-α: pegylated interferon alfa 2b and pegylated interferon alfa 2a. Pegylated interferon 2b consists of a straight chain 12 kd PEG attached to the histidine residue. Pegylated interferon 2a consists of a branched-chain 40kd PEG attached to lysine residue.

Data from the international multi-center trial of 1,219 treatment-naïve patients with chronic HCV randomized to either interferon alfa-2b 3 MU TIW or one of the three weight-based doses (0.5, 1.0, or 1.5 mcg/kg per week) of pegylated interferon alfa-2b for 48 weeks were recently reported. At all doses, pegylated interferon alfa-2b was more effective than standard interferon alfa-2b. Multivariate analysis revealed that HCV genotype 2 or 3 infection had a higher sustained viral eradication rates than HCV genotype 1. The safety profile and tolerability of those regimens were similar.

In another large-scale trial, patients treated with pegylated interferon alfa-2a (180 mcg per week dose) were compared with high-dose IFN-α 2a (six MU three times a week for three months followed by three MIU for nine months). The study revealed a SVR of 39 percent for pegylated interferon alfa 2a versus 19 percent with standard interferon alfa-2a. HCV genotype, viral level, age and the stage of fibrosis were important predictors of response to therapy.

In hopes of obtaining long-term survivals that are similar to those seen with other diagnoses, the current trend is to better identify the role of antiviral therapy on the post-transplant disease process.

Similar to studies of standard IFN-α, the addition of ribavirin to pegylated interferon-α seems to enhance their efficacy. In the trial of pegylated interferon alfa-2b and ribavirin for previously untreated patients (n=1530), 62 percent viral clearance at the end of treatment with a sustained virologic response of 54 percent were noted. Patients with genotype 1 who were treated with 1.5mcg/kg per week of pegylated interferon alfa-2b plus 800 mg/d ribavirin had a 42 percent SVR, as compared to 81 percent for those with genotypes 2 or 3.

In another recently reported trial, the efficacy of pegylated interferon alfa-2a and ribavirin was compared to standard interferon alfa-2b and ribavirin, as well as pegylated interferon alfa-2a monotherapy. In this large trial of 1,121 previously untreated HCV patients, pegylated interferon alfa-2a and ribavirin were associated with 56 percent SVR as compared to 44 percent SVR with standard interferon alfa-2b and ribavirin combination and 30 percent with pegylated interferon alfa-2a alone. Again, those with HCV genotype 1 were treated with PEG-IFN and ribavirin combination achieved 46 percent SVR as compared to 76 percent for genotype 2 or 3. Both of these trials suggest that combination of pegylated interferon alfa and ribavirin will be associated with an enhanced SVR rate of greater than 50 percent.

In summary, a combination of standard IFN-α plus ribavirin is currently associated with a 35-40 percent SVR. With the new regimens of pegylated interferons and ribavirin, over 50 percent sustained virologic response is possible. As the efficacy of newer regimens improves, additional steps to adequately manage their side effects and maximize adherence to these regimens have become crucial.

HEPATITIS C AND LIVER TRANSPLANTATION

Since it was first identified 13 years ago, hepatitis C has now become the most common indication for liver transplantation in both the United States and Europe. Over 30 percent of all transplants performed are now for chronic liver disease secondary to hepatitis C. Unfortunately the recurrence of viremia is universal following liver transplantation, with 20 percent of patients developing cirrhosis in their new allograft by the fifth postoperative year. Despite the high rate of recurrence, patient survivals are not dissimilar to survivals seen after transplant from other diagnoses at five years, but by 10 years they are significantly worse than expected. It has also become increasingly clear that retransplantation may not be an option, as recurrence appears to be more aggressive with short and long-term survival below what is expected.

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is to better identify the role of antiviral therapy on the post-transplant disease process. Three trials published in the late 1990's looked at early treatment of transplant patients using IFN alpha-2b monotherapy. None of these studies showed a significant, sustained virologic response at 12 months or improvement in either patient or graft survivals.

The efficacy of combination therapy with ribavirin and interferon has been reported by several centers since 1997. Twenty seven to 53 percent of patients exhibited a virologic response at the end of 12 months of treatment, but only 17 to 27 percent were sustained. Side effects, mainly severe anemia, were common with 20 to 50 percent of patients needing to stop therapy for serious drug related events.

With the recent release of the pegylated form of interferon (PEG), there is new hope that post transplant patients may have better options for treatment. Initial studies with PEG monotherapy shows 36 percent of patients had undetectable HCV RNA levels with only seven percent of patients withdrawing from the study because of unacceptable side effects. Small studies involving combination therapies with ribavirin indicate an over 50 percent sustained response rate, but the combination was not well tolerated. Genotype remains the most important predictor of a sustained response. It needs to be mentioned that these studies are preliminary, and additional data will need to be obtained before a standardized recommendation can be made.

Despite the advances in antiviral therapy, it is likely that treatment of the disease after it has recurred will result in sub-optimal outcomes in a large percentage of the post-transplant population. This has led to renewed interest in trying to prevent the recurrence of viremia following transplant. Charlton and Pelletier have shown that the severity of recurrence following transplant is related to the viral load at the time of transplant. This has raised the question as to weather actively reducing viral load at the time of transplant could improve outcome.

There would be two logical ways to reduce viral load, mechanical or immunologic. The mechanical options would use filters to reduce the viral load within the plasma, but it would be unlikely to result in a complete elimination of the virus. The development of antibody preparations targeting hepatitis C could also theoretically reduce the viral load if administered during and after the anhepatic phase of the liver transplant.

A polyclonal hepatitis C immunoglobulin has been used in patients undergoing transplantation. Unfortunately the polyclonal antibodies exhibited no effect on either clinical or virological recurrence of hepatitis C in the 20 patients studied. Monoclonal antibodies have historically had greater efficacy than their polyclonal counterparts. Several new monoclonal antibodies against hepatitis C are currently being developed in hopes of identifying a preparation effective enough to prevent the recurrence of hepatitis C following transplantation. Over the next few months, the Inova Fairfax Transplant Center will be one of the few U.S. centers participating in a trial of monoclonal anti-HCV antibodies used for liver transplant patients with HCV.

The decision as to which transplant patients to treat, when to treat them and with what drug combinations, is becoming increasingly difficult. One recommendation is that any post-transplant patient who has virologic recurrence and elevation in their aminotransferases should undergo liver biopsy. Those with moderate to severe inflammatory change that is consistent with recurrence of hepatitis C or fibrosis should be considered for treatment with PEG interferon, low doses ribavirin and close monitoring for side effects. The final treatment strategies for prevention of HCV in post-transplant patients await better results of the ongoing clinical trials. ■

RESEARCH PROTOCOLS

The following is a list of the research protocols at the Center for Liver Diseases at Inova Fairfax Hospital:

- Growth factors for treatment of cytopenia in patients with hepatitis C on Ribavirin/PEG-IFN.
- The use of Interferon Gamma-1b as an anti-fibrotic agent in hepatitis C.
- Pegylated interferon Alpha 2b maintenance protocol for prevention of complication of HCV-related cirrhosis.
- Monoclonal Anti-HCV for prevention of post-transplant HCV.
- Pravachol for treatment of hyperlipidemia in patients with liver disease.
- Epidemiology for hepatitis B in the United States.
- Epidemiology of hepatocellular carcinoma in the United States
- Epidemiology of Non-Alcoholic Fatty Liver Disease.
- Efficacy trials in Non-Alcoholic Fatty Liver Disease.

For patient screening or additional information, please call the Center for Liver Diseases at **703-698-3182**, or fax **703-698-3481**.

American Liver Foundation Corner

Hepatitis C Support Groups

Inova Fairfax Hospital and the ALF sponsor Hepatitis C Support Groups in the Washington, DC area. The group will meet at the hospital in conference rooms D, E and F on the following dates:

- **February 18**
- **March 18**
- **April 15**

Publications and Presentations

PUBLICATIONS

- L Siatkosky, K Shermock, Z Younossi. "Investigational pharmacologic treatment for liver disease" *Expert Opinion on Investigational Drugs* 2002.

PRESENTATIONS

- Triple Combination of Pegylated Interferon Alpha 2b, Ribavirin and Amantadine for Treatment of Chronic Hepatitis. SHINE Meeting Huntington Beach, CA.
- The Spectrum of Nonalcoholic Fatty Liver Diseases (NAFL); Clinical Research Single Topic Conference on Nonalcoholic Steatohepatitis (NASH); American Association for the Study of Liver Diseases, Atlanta, GA.
- Nonalcoholic Fatty Liver Disease (NAFL) Abstract Presentations; The Liver Meeting. American Association for the Study of Liver Diseases, Boston, MA.

APPOINTMENTS

- Medical Advisory Chairman, 2003, The American Liver Foundation, Washington D.C. Chapter
- Associate Editor, 2002, *Liver International*

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.

www.inova.org

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