

# Liver Update

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

## Chronic Hepatitis C: An Update on Treatment Options

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Hepatitis C virus (HCV) infects an estimated two to three million people in the United States and 175 million people globally. Of those infected, 75 to 80 percent develop chronicity. Most patients remain asymptomatic despite silent, insidious progression to cirrhosis, which is estimated to occur in 20–25 percent, and account for 8–10,000 deaths annually in the United States. This makes HCV the leading indication for liver transplantation. In addition to its clinical impact, HCV can have an enormous economic impact.

Over the last decade, tremendous gains have been made in our understanding and treatment of HCV. Each new development in hepatitis C treatment has improved our ability to treat patients more successfully. In the early 1990s, with the advent of interferon monotherapy, we were able to eradicate the HCV in only 10–15 percent of patients. Two comparative trials of interferon and ribavirin combination in the previously untreated HCV patients suggested 31–43 percent viral eradication rates.

In these trials, HCV genotype was found to be the most useful determinant of response. Patients with genotype 2 or 3 had excellent response rates, with almost 60 percent achieving virologic clearance. Comparatively, HCV genotype 1 is more difficult to treat. Very few patients with HCV genotype 1 would respond to treatment with interferon monotherapy, but 29 percent achieved virologic clearance with 12 months of the two-drug combination.

In a subsequent re-analysis of this data, patient and viral factors were used to develop an “a la carte” regimen for treatment of these patients. It subsequently became evident that patients receiving more than 80 percent of the combination regimen’s dose and completing 80 percent of the duration of therapy can achieve the best viral eradication rates.

Re-treatment of patients who are non-responsive to interferon monotherapy or combination therapy is more problematic. Using interferon and ribavirin to retreat these patients has been associated with five to 20 percent sustained virologic response (SVR). Interferon alone, or in combination with other oral agents, are not associated with

*see CHRONIC HEPATITIS C, page 2*

*A number of clinical trials for treatment of HBV, HCV and non-alcoholic steatohepatitis (NASH) are available at the Center for Liver Diseases. For more information, call 703-698-3182.*

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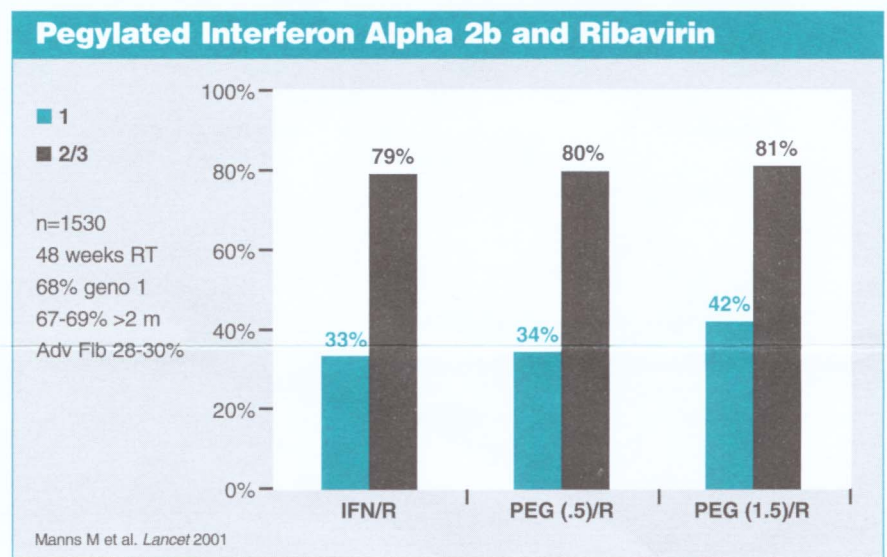
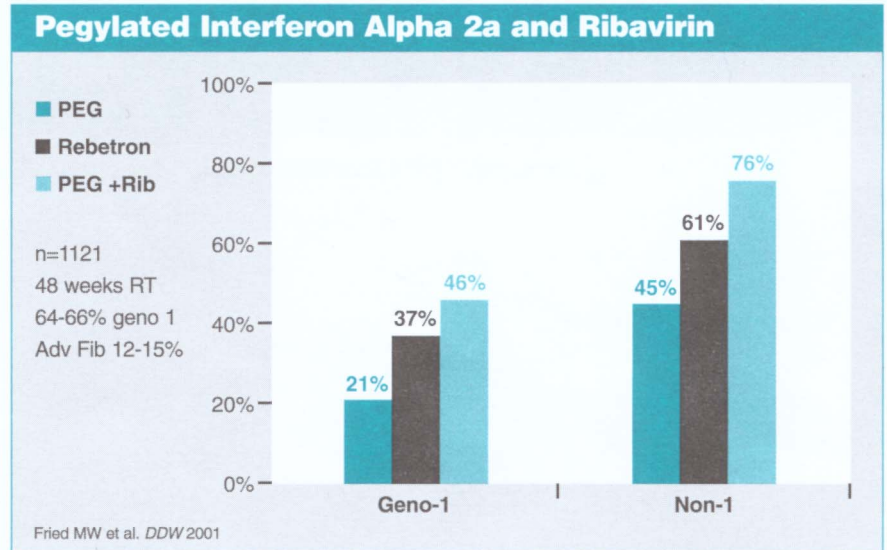


enhanced efficacy. Additionally, induction regimens do not seem to be beneficial. However, a three drug regimen (interferon, ribavirin and amantadine) remains promising.

In addition to the development of better combination regimens, better understanding of HCV and its viral kinetics have lead to some important advances.

The effect of interferon on the kinetics of HCV suggests that viral suppression can be achieved more efficiently if a sustained level of interferon can be delivered. Additionally, fluctuating level of viremia, which occurs with every other day dosing, may contribute to the ability of the virus to develop "escape mutants" and become resistant to the treatment. In an attempt to address these issues, pegylated formulation of interferon, which provides a more uniform plasma level and more efficiently suppress the virus, has been developed. The attachment of a polyethylene glycol to interferon improves its half-life, leading to only weekly injections. Two pegylated products (pegylated interferon alpha-2b and pegylated interferon alpha-2a) have been developed and tested in large, randomized clinical trials. Preliminary data suggest that pegylated products result in doubling the rate of SVR of their respective standard interferons. However, combining pegylated interferon alpha-2b with ribavirin suggests a 47-54 percent SVR. This efficacy seems to be higher in those who were able to complete a higher dose of interferon and ribavirin. In a separate study of pegylated interferon alpha-2a and ribavirin, similar viral eradication rates were reported. (Figures)

Although the response rate to combination therapy is still modest, those with a sustained response to therapy will have a durable response. Follow-up studies of patients treated with interferon monotherapy and interferon/ribavirin combination therapy



indicate that 95-99 percent remain in remission four to 10 years later.

It is important to remember that the minimal criteria for treating candidates with interferon-based therapy are the absence of contraindications. Furthermore, patients treated with interferon and ribavirin combination should be monitored for compliance and development of side effects. It is crucial that physicians treating HCV are familiar with the management of interferon-induced side effects, such as bone marrow suppression, flu-like syndrome, thyroid disease, as well as the development of neuropsychiatric side effects such as depression and anxiety. Pegylated interferon products seem to have similar side effect profiles to their

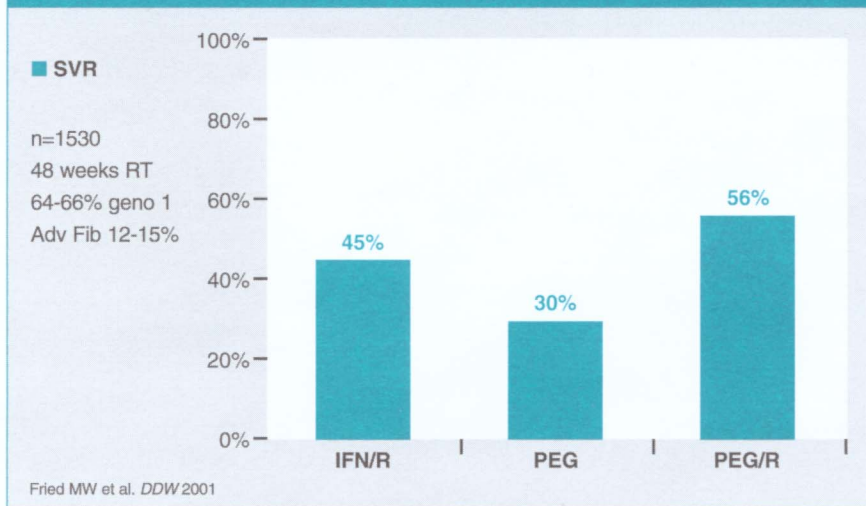
standard interferon counterparts. Although the addition of ribavirin does not enhance the interferon side effects, it has its own array of potential side effects, including dose-dependent hemolysis and potential for teratogenicity, both necessitating additional monitoring.

In addition to the development of pegylated interferon and ribavirin combinations, other innovative approaches to the treatment of HCV are being developed. These include the following:

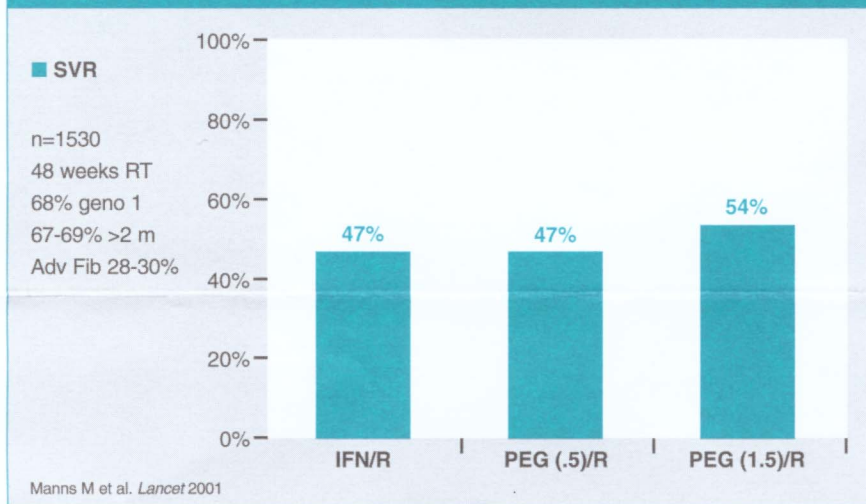
- Molecular approaches to HCV treatment: Viral enzyme inhibitors that could block the HCV enzymes protease, helicase and



## Pegylated Interferon Alpha 2a and Ribavirin



## Pegylated Interferon Alpha 2b and Ribavirin



polymerase to prevent viral replication and other molecular-based approaches, including hammerhead ribozymes and antisense oligonucleotides, which also prevent replication of the virus are in development phases. Although several potential candidates, these agents are in the very early phases of development and will not be available in the near future.

Immunomodulatory approaches to HCV: Interleukin 10 (IL-10) has no anti-viral activity, but can have antifibrotic effect. A small short-term trial of this agent has shown promising results. In addition to IL-10, interferon gamma 1b is also being tested as a potential anti-

brotic agent in HCV. Details of the impact of these agents and other antifibrotic agents (colchicine, long-term maintenance pegylated interferons, etc) on natural history of HCV are not available.

In summary, the last decade has witnessed tremendous gains in our understanding of HCV, its potential epidemiologic/clinical impact and its treatment. As we enter the new century, it remains crucial that patients, physicians and other health care workers are up to date on the new information regarding this important chronic disease and are familiar with the newer regimens that are being developed to treat it.

## Health-Related Quality of Life (HRQL) and Chronic Liver Disease

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Quality of life as an outcome variable has become an important measure in clinical research. This is in part due to the transition from a "biomedical model" of health to the one that incorporates both the clinical and social aspects of disease. Clinicians and researchers dealing with chronic illnesses now incorporate quality of life measures into their clinical practice and research. Research has shown that chronic liver disease has a significant impact on patients' well-being and contributes to morbidity associated with these conditions.

Various conditions are encompassed within the term "chronic liver disease" and with these conditions come varying effects on individuals' HRQL. For example, patients in the early stages of disease typically exhibit few or non-specific symptoms (such as fatigue, pruritis) with some effect on HRQL. However, as the disease progresses and the complications of cirrhosis present themselves (such as ascites, portal hypertension, and hepatic encephalopathy) patients report notable effects on HRQL.

### IMPACT OF LIVER DISEASE ON HRQL

The impact of liver disease on HRQL is multifaceted, encompassing a multitude of issues. Research predominantly shows that the presence of chronic liver disease produces a reduction in HRQL. Topics such as disease severity, type



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of disease, demographics (age, gender, etc.), route of transmission of viral hepatitis, alcohol, and comorbid conditions have been addressed in the literature.

A recent large-scale study examining the impact of type and severity of chronic liver disease on HRQL found that chronic liver disease considerably reduces HRQL, however, this impact does not appear to differ significantly by type of disease. There were some measures of disease severity associated with these impairments, such as higher Child-Pugh class. Additionally, older age appeared to be associated with lower HRQL scores.

The presence of comorbid conditions can often complicate the impact of liver disease on HRQL. A recent study of patients with chronic hepatitis C (HCV) examined the relationship between a past history of substance abuse, current medical/psychiatric comorbidities and patients' HRQL. The authors found that a past history of substance abuse did not correlate with any of the HRQL measures. However, there was a significant correlation between current medical comorbidities (especially painful medical conditions and a depressed mood) and HRQL scores. The authors concluded that although these two conditions may account for some of the decline in HRQL of patients with HCV.

An important area of research is the impact of diagnosis of HCV on patients' HRQL. The majority of research on chronic liver disease and HRQL has focused on the clinical and/or physical effects of the disease on patients' well-being. However, as we frame chronic liver disease, especially viral diseases such as hepatitis C, in more of a social context, it becomes important to examine how the knowledge of a positive diagnosis can affect HRQL. In a recent study, a cohort of individuals admitted to the hospital with acute hepatitis who were aware of their seropositive status

reported significantly poorer quality of life than those individuals who were unaware. One hypothesis is that it is possible that the knowledge of having a chronic, potentially transmissible and lethal disease negatively affects patients' HRQL. The significance of this was recently reinforced by another study, which examined the cost-effectiveness of screening strategies for HCV.

The impact of dis-utility of knowledge of HCV diagnosis was assessed using Markov modeling. The authors found that the most important variable negatively impacting incremental cost-effectiveness ratios of screening average risk individuals for HCV was the loss in utility, or quality of life, related to the knowledge of a positive HCV test result. Therefore, it is possible that the psycho-social impact of establishing the diagnosis of HCV (anxiety, social stigma, and uninsurability) have a profound negative impact on patients' HRQL.

#### IMPACT OF "THERAPY" ON HRQL

Liver transplantation is one of the most drastic interventions or "therapies" for patients with very advanced liver disease. Research shows that those who receive a liver transplant have not only improvements in their survival (one-year survival rate of 80-85 percent) but also in their HRQL. The measurement of HRQL as an outcome has become an integral piece of the post-transplant evaluation and is being closely monitored by clinicians. Additionally, recent data suggest that a rapid improvement of HRQL post-OLT may be associated with better resource utilization.

In addition to OLT, other therapies not as drastic, such as the therapy regimen for chronic hepatitis C, can have favorable impact on HRQL. Pegylated interferon plus ribavirin is the current therapies for HCV and various studies have evaluated the impact of such therapies on HRQL. Research shows that patients with

chronic hepatitis C report more impairment in HRQL than the population norms prior to the initiation of treatment. Although this impairment is exacerbated during the course of therapy, once viral eradication is achieved, an improvement in HRQL can be documented.

One could argue that the decision about whether or not to treat patients should take into consideration not only clinical data (presence of cirrhosis, HCV genotype, etc.) but also the impact of therapy on HRQL. We know that those with chronic liver disease and hepatitis C specifically, have impaired HRQL. We also know that the current antiviral therapy for hepatitis C worsens this impairment during active treatment. However, recent data shows that those who sustain a virologic response report significant improvements in HRQL. So the long-term benefits of therapy (eradicating the virus) are possibly worth the short-term impairments in HRQL. However, this needs to be with careful monitoring of side effects, including the psychiatric side effects of interferon with potential negative impact on a patient's HRQL.

#### CONCLUSION

In summary, the concept of quality of life has been through a transition in the last 50 years, moving from measuring strictly a state of physical health to now encompassing the psychosocial aspects of disease. The utilization of quality of life measures in clinical research with chronic illness has become commonplace. Research on patients with chronic liver disease illustrates the significant impairments that these patients experience. The continued incorporation of HRQL measures into clinical practice will further enable clinicians to develop patient-oriented treatment strategies.



## RESEARCH PROTOCOLS

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

- Pegylated Interferon Alfa 2b and Ribavirin for chronic hepatitis C.
- Triple regimen of Pegylated Interferon Alfa 2b, Ribavirin and Amantadine for treatment of chronic hepatitis C.
- Pegylated Interferon Alfa 2a in combination with Ribavirin for chronic hepatitis C.
- 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 2a with or without Thymosin Alpha 1 for chronic hepatitis C.
- Immunomatrix evaluation of rapid one-step immunoassay for HCV.
- Lamivudine with or with out monoclonal HBV antibody for chronic hepatitis B.
- Adefovir Dipivoxil for the treatment of hepatitis B.
- Emtricitabine for chronic hepatitis B.
- 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**.

## Publications and Presentations

### PRESENTATIONS

- "Health-Related Quality of Life and Liver Transplantation", Transplant Grand Rounds, UCLA, December 2001.
- "An Update on NASH", Medical Grand Rounds, Inova Fairfax Hospital, January 2002.
- "NASH and Hepatitis C", Cornell University, January 2002.
- "Viral Hepatitis", GI/Liver Wrap-Up Course, University of Michigan, February 2002.

### PUBLICATIONS

- KM Shermock, ME Temple, Z Younossi. "A Pharmacoeconomic Appraisal of Therapies for Hepatitis B and C". *Expert Opinion of Pharmacotherapy* 2(2):205-211, 2001.
- C Broussard, A Aggarwall, S Lacey, T Post, T Gramlich, M Henderson, Z Younossi. "Mushroom Poisoning: From Diarrhea to Liver Transplantation". *American Journal of Gastroenterology* 96(11):3195-3198, 2001.
- M Singer, Z Younossi. "Cost-effectiveness of Screening for Hepatitis C Virus in Asymptomatic, Average Risk Adults: Has the Time Come?" *American Journal of Medicine* 111:614-621, 2001.
- L Martin, K Irwin, Z Younossi. "Health-Related Quality of Life and Chronic Liver Disease: Conceptual Challenges and Clinical Applications." *Clinical Perspectives in Gastroenterology*, In Press, January/February 2002.
- L Martin, M Sheridan, Z Younossi. "The Impact of Liver Disease on Health-Related Quality of Life: A Review of the Literature." *Current Gastroenterology Reports* Vol 4 Issue 1: 2002 In Press.

Also, Zobair Younossi, MD, has been asked to serve on the Editorial Board of *Hepatology*, the leading journal in the field of hepatology.



## American Liver Foundation Corner

The Greater Washington, DC, Chapter of the American Liver Foundation is eager to be of service to you and your patients. Over the past year, our constituent services have grown quite a bit. Our programs have expanded to include patient educational meetings, support groups, and a very well received newsletter. The continued growth of the chapter is vested in the resources and expertise provided by an energetic board of directors.

Physicians have been and remain a vital resource as we build this board and the chapter. If you or someone you know in the liver disease/transplant communities, whether a patient, physician, affected family member or other, desires to make a difference in the fight against liver disease, please call or refer them to us. Your support is essential. We can be reached at **202-872-6600** or via e-mail at **alfdc@starpower.net**. I look forward to working with you.

*Yao P. Tyus,  
chapter director*

Inova Health System is a not-for-profit health care system in Northern Virginia that consists of hospitals and other health services including home care, nursing homes, mental health services, physician practices, wellness classes, and freestanding emergency and urgent care centers. Governed by a voluntary board of community members, Inova's mission is to provide quality care and to improve the health of the diverse communities we serve.

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