

ribavirin and amantadine) has recently shown encouraging results.

How about patients with persistently normal ALT?

The majority of patients with truly persistent normal liver enzymes have mild histologic findings, although some may have significant fibrosis. To date, there is no convincing data to suggest that interferon monotherapy achieves a significant viral eradication. Although still preliminary, it seems that interferon + ribavirin combination may achieve reasonable rates of viral eradication.

WHAT LIES AHEAD?

Many innovative approaches to the treatment of HCV are being developed. They include:

- **Pegylated interferon**, a long-acting, synthetic form of interferon given as a weekly injection. Two pegylated interferon products are being tested. These products improve the pharmacokinetics of interferon while retaining anti-viral activity. These regimens use weekly injection and seem to have similar side effect profiles. In two large multi-center studies of pegylated interferons, the viral eradication rates doubled that of their respective standard interferon regimens. It seems that pegylated

interferon monotherapy will be associated with 25–35 percent viral eradication rates. The addition of ribavirin to pegylated interferon is estimated to increase viral eradication rates to approximately 50–55 percent.

- **Interleukin 10 (IL-10)** has been used to treat patients with chronic hepatitis C who are considered non-responders to previous therapy. Although, IL-10 has no anti-viral activity, it did result in significant histologic improvements with little side effects. Longer courses of IL-10 or combination regimens using IL-10 with other antiviral agents are underway.

Viral enzyme inhibitors that could block the HCV enzymes protease, helicase and polymerase to prevent viral replication and **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. Finally, **immunotherapy approaches**, including T-cell-based immunotherapy, either antigen specific or nonspecific; and strategies that efficiently deliver antiviral cytokines to the liver by adenoviral vectors or by liposomes are also being developed which can broaden our ability

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ty to treat patients with chronic hepatitis C.

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Liver Update

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An Update on Treatment Options for Chronic Hepatitis C

Hepatitis C virus (HCV) infects an estimated 2-3 million people in the United States and 175 million people globally. Over 80 percent of infected patients develop chronic disease. Most patients remain asymptomatic despite silent, insidious progression of the disease.

The sequelae of HCV-induced chronic liver disease accounts for 8-10,000 deaths annually in the United States and currently is the leading indication for liver transplantation. It seems that HCV is more aggressive in those who consume excessive amounts of alcohol. Additionally, disease may be more aggressive in individuals who acquire it at an older age and in male patients.

Over the last decade, tremendous gains have been made in our understanding of HCV with the development of increasingly effective therapeutic modalities to treat this disease. Each new development in hepatitis C treatment has improved our ability to treat patients successfully; as recently as 10 years ago, no treatment was available. With the advent of interferon therapy, we were able to eradicate the hepatitis C virus in approximately 10 to 15 percent of patients. The combination therapy with interferon alfa-2b and ribavirin helps us achieve sustained viral eradication in about 40 percent, yet leaving the other 60 percent with no effective treatment available.

WHAT WE KNOW ABOUT TREATMENT

Patient Selection

The minimal criteria for candidates for interferon-based therapy are the presence of elevated liver enzymes, a detectable HCV RNA and some histologic activity. Additionally, there should be no contraindication to interferon therapy and patients should be monitored for compliance with therapy. It is crucial that physicians treating patients with hepatitis C with interferon products are aware of side effects and are familiar with their management. These include bone marrow suppression, flu-like syndrome and thyroid disease. Neuropsychiatric side effects of interferon may include depression and anxiety, which require close monitoring.

Drawbacks of combination therapy

Although ribavirin does not seem to enhance the interferon induced side effects, it has its own array of potential side effects: dose-dependent hemolysis and potential for teratogenicity. The combination of interferon and ribavirin is contraindicated in patients who have significant anemia, hemolysis, renal insufficiency, coronary artery disease, cerebral vascular disease, gouty arthropathy, or who are unable to practice contraception. Other less severe adverse effects include rash, itching, insomnia, dyspnea and cough.

NEWER STUDY RESULTS

Two comparative trials of interferon monotherapy and combination interferon and ribavirin that provide two-year results for a cohort of 1,744 patients provide much of

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the data to date. It seems that the combination of interferon alpha 2b and ribavirin resulted in sustained viral eradication in 31–43 percent of previously untreated patients. In this trial, HCV genotype was found to be the most useful determinant of response. Patients with genotype 2 or 3 had an excellent response rate: almost 60 percent achieved virologic clearance with combination therapy. Furthermore, their response rate with six months of treatment was often as good as their response rate with 12 months of therapy.

Comparatively, genotype 1 patients were found to be the most difficult to treat. Very few of them had responses to treatment with interferon alone, but a relatively high proportion, about 29 percent, achieved virologic clearance with 12 months of therapy with the two-drug combination. In a subsequent re-analysis of this data, it has been suggested that genotype as well as other factors can be used to determine an “a la carte” regimen for patients with chronic hepatitis C.

Finally, it is becoming evident that patients who receive more than 80 percent of the combination dose regimen and complete over 80 percent of the duration of therapy seem to benefit the most.

OPEN PROTOCOLS

The following protocols are open for patient enrollment at the Center for Liver Diseases:

- Pegylated Interferon alfa 2b and Ribavirin for chronic hepatitis C, previous treatment failures.
- Triple regimen of Pegylated Interferon alfa 2b, Ribavirin and Amantadine for treatment of chronic hepatitis C
- Adefovir dipivoxil for the treatment chronic hepatitis B.
- Pegylated Interferon alfa 2a (PEGASYS) alone or in combination with Ribavirin for chronic hepatitis C.
- Immunomatrix Evaluation of a rapid one step immunoassay for HCV.

For patient screening or additional information, please call Peggy Kraft at **703-204-6491**.

Is the response to therapy durable?

Although the response rate to interferon monotherapy is low, and the response to combination therapy is still modest, those patients who have a sustained response to therapy will have a durable response. Follow-up studies of patients treated with interferon monotherapy indicate that 95 percent remain in remission 5 to 10 years later. We anticipate the five-year viral clearance rate for those who respond to combination therapy will be about 95 percent.

Are we overtreating with combination therapy?

Should certain individuals still be treated with interferon alone? When five factors associated with enhanced response rate were considered (presence of genotypes 2 or 3, low viral load [< 2 million copies/ml], absence of cirrhosis, female gender, and age younger than 40 years), across the board, patients achieved a significantly better sustained response rate when treated with the two-drug combination. Interferon monotherapy should still be considered for those patients with a contraindication to ribavirin.

IMPLICATIONS FOR TREATMENT

For patients who are considered candidates for treatment, one treatment strategy is as follows:

- Consider ordering HCV genotype testing to determine the duration of therapy. Treat patients with genotype 1 for 12 months (if HCV RNA is undetectable after six months of therapy) and patients with genotypes 2 or 3 to six months.
- Measure HCV RNA at week 24 to predict virologic response.
- Monitor the hemoglobin level, because ribavirin treatment causes hemolytic anemia, which can be managed with dose modifications.
- Order pregnancy testing and have the patient use contraception, because ribavirin is potentially teratogenic.
- Monitor for neuropsychiatric side effects of interferon, such as depression and anxiety on a regular basis.

Re-treatment of patients

An option for retreating patients who initially respond to interferon treatment but who suffer a relapse is to re-treat with the combination therapy. Adding ribavirin to interferon significantly enhances the response rate in patients who have experienced a relapse. One study using high dose consensus interferon achieved relatively high response rates. Although encouraging, this study has not been replicated with the other interferon monotherapy regimens.

Re-treatment of patients who are non-responsive to interferon monotherapy is problematic. Using interferon monotherapy or combining these regimens with other oral agents is not associated with enhanced efficacy. Additionally, induction regimens do not seem to be beneficial. Using interferon ribavirin regimen has been associated with sustained viral eradication rates ranging between 5–20 percent. It seems that this regimen used for truly interferon non-responder individuals can be associated with a 10–15 percent viral eradication. In an attempt to enhance efficacy a regimen of three drugs (interferon,

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MELD Scoring System: New Criteria for Prioritizing Liver Transplant Candidates

UNOS has recently issued a policy proposal to establish new status criteria for prioritizing liver transplant candidates with pre-existing liver disease. The policy proposed would replace the current Status 2A, Status 2B and Status 3 medical urgency categories with a continuous numerical scale which determines a patient's risk of mortality on the waiting list.

Patients would be prioritized for liver allocation based on a risk score calculated from a model developed by the Mayo Clinic (Mayo Clinic End Stage Liver Disease Model) which utilizes the prognostic factors of creatinine, bilirubin, prothrombin/INR and disease etiology. This new system would de-emphasize waiting time as a factor in liver allocation since it has been demonstrated that it does not correlate with death while waiting for transplant. The rules pertaining to Status 1 patients would remain unchanged.

The current Child-Turcotte-Pugh (CTP) system has come under criticism for the following reasons:

- It was designed to assess the risk of mortality for patients undergoing surgical portocaval shunt or esophageal transection for variceal bleeding.
- The majority of patients studied were alcoholic cirrhotics and not representative of the spectrum of liver disease.
- It does not significantly differentiate among patients in terms of the severity of a particular clinical factor – the CTP system assigns three points to a patient with a bilirubin > 3 but does not differentiate between a patient with a bilirubin of four and one with a bilirubin of 20 even though the latter patient has a higher mortality rate.

- Ascites and encephalopathy are subjective criteria and open to manipulation.
- CTP does not take into account renal function, which is one of the most important factors influencing pre- and post-transplant patient survival.

The MELD model, using creatinine, bilirubin, INR and disease etiology, can accurately predict patients who have a median survival of three months after elective TIPS. The MELD model was validated outside the United States in liver disease patients undergoing TIPS and here in the U.S. in hospitalized cirrhotics, outpatient cirrhotics, SBP patients and UNOS waiting list patients. It was also applied to a group of liver transplant recipients but was not useful in predicting survival in this group, probably because many factors are involved including factors related to the graft itself.

The numerical scale is based only on objective data (creatinine, bilirubin, INR, disease etiology) and subjective data such as intractable ascites and encephalopathy are excluded. Once the scale is developed, it would be used to offer livers to patients based on medical urgency. To differentiate patients in the same severity category, total waiting time accumulated in that category or any category of greater severity would be used as a tiebreaker. Waiting time would still be a factor but with less emphasis than under the current system.

The MELD score is calculated by combining the four prognostic factors with their regression coefficients: $R = 0.957 \times \text{Loge}(\text{creatinine mg/dl}) + 0.378 \times \text{Loge}(\text{bilirubin mg/dl}) + 1.120 \times \text{Loge}(\text{INR}) + 0.643 \times (\text{etiology})$. 0 is used for alcohol related liver disease and 1 for all other causes. The risk score is then rounded to the tenth decimal place

and multiplied by 10 (eg $2.073 = 21$). This formula is available online with instant calculation.

Patients with more severe disease that is not reflected in the MELD score will require review board consideration, as is currently performed, e.g. patients with hepatopulmonary syndrome. Other groups requiring special consideration are those patients with HCC and pediatric patients. Investigations are underway to modify the model for pediatric patients. For those patients with HCC who are currently allocated a 2B status, it is recommended that they are allocated a MELD score (yet to be determined) which is augmented at three monthly intervals as their metastatic tumor workup is shown to be negative.

For the majority of patients, the MELD score can be updated as laboratory values change. The current recommended schedule for recalculation is as follows: MELD score <10 – yearly update; 10-20 – 6 months update; 21-30 – 3 months update; >30 – weekly or less. Compliance would be monitored by computer printouts of laboratory data and on site monitoring, which is the current surveillance.

Following the recent public forum on this new system, it is clear that the system will change. The precise details are not yet available and the MELD system as described above may require modification, particularly with regard to serum creatinine and body weight and gender, and disease etiology. Before being implemented nationwide, several groups have suggested that it be implemented for a trial period in a single region.

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