Response to treatment is defined as undetected HCV RNA and normalization of ALT levels at 24 weeks post treatment. Response rates to the 1.0 and 1.5 μg/kg Pegylated Interferon doses were similar (approximately 24%) to each other and were both higher than the response rate to INTRON A (12%).

Patients infected with HCV genotype 1, and patients with high baseline levels of HCV RNA (more than 2 million copies per ml of serum); were less likely to respond to treatment with Pegylated Interferon.

Patients receiving Pegylated Interferon with genotype 1 had a response rate of 14% while patients with other viral genotypes had a 45% response rate.

Ninety-six percent of the responders in the Pegylated Interferon groups and 100% of responders in the INTRON A group first cleared their viral RNA by week 24 of treatment.

Combination Treatment – A randomized study compared treatment with two PEG-Intron/REBETOL regimens [PEG-Introm 1.5 μg/kg SC once weekly (QW)/REBETOL 800 mg PO daily (in divided doses); PEG-Intron 1.5 μg/kg SC QW for 4 weeks then 0.5 μg/kg SC QW for 44 weeks/REBETOL 1000/1200 mg PO daily (in divided doses)] with INTRON A (3 MIU SC thrice weekly (TIW)/REBETOL 1000/1200 mg PO daily (in divided doses).

Response to treatment is defined as undetected HCV RNA and normalization of ALT levels at 24 weeks post treatment. The response rate to the PEG-Intron 1.5 μg/kg plus ribavirin 800 mg dose was higher that the response rate to INTRON A/REBETOL. The response rate to PEG-Intron 1.5 → 0.5 μg/kg/REBETOL was essentially the same as the response to INTRON A/REBETOL.

Patients with viral genotype 1, regardless of viral load, had a lower response rate to PEG-Intron (1.5 mg/kg)/REBETOL compared to patients with other viral genotypes. Patients with both poor prognostic factors (genotype 1 and high viral load) had a response rate of 30% (78/256) compared to a response rate of 29% (71/247) with INTRON A/REBETOL.

Attachment C

HCV Evaluation and Treatment Consent Form

I _____ _____
PATIENT'S NAME ID NUMBER

consent to the evaluation and potential medication administration, or continuation of a current treatment regimen initiated outside of this facility, for Hepatitis C based on the information provided, explaining the risks and potential benefits consistent with the manufacturer's recommendations.

I understand that treatment consists of injections of an interferon product up to three times per week and may include ribavirin pills to be taken two times daily for 6 to 12 months. I understand that treatment also involves multiple visits to obtain blood for laboratory testing necessary for ongoing monitoring. I understand that there is no data regarding whether interferon product treatment will prevent transmission of Hepatitis C virus to others. Also, it is not known if treatment with an interferon product will cure Hepatitis C or prevent cirrhosis, liver failure, or liver cancer that may be the result of infection with the Hepatitis C virus. Furthermore, I understand that even if the Hepatitis C treatment is successful in eliminating the virus, if I engage in high-risk behaviors, I may become re-infected with Hepatitis C.

Currently, an interferon product and ribavirin combination treatment represents the best option for clearing the virus from your blood. Many patients do not respond to this treatment. If you do not respond the medications will be discontinued. Treatment for Hepatitis C may have serious side effects, including worsening of liver inflammation, anemia, allergic reaction, heart attack, severe depression, suicide, pneumonia, loss of vision, or thyroid disease. Most people who are treated for Hepatitis C have flu-like symptoms that are sometimes very uncomfortable. These symptoms include fever, headache, chills, sore muscles, fatigue, nausea, vomiting, diarrhea and loss of appetite. Approximately 10% to 15% of people receiving this treatment stop because of side effects. The side effects, however, can be severe enough to result in death. Birth defects may occur if either parent is undergoing treatment for Hepatitis C at the time or within six months before a pregnancy begins.

Compliance is an essential component of the treatment for Hepatitis C. I understand that I must follow the established treatment plan and that treatment may be discontinued if I do not comply. Treatment consists of directly observed therapy.

I understand that I should not initiate a pregnancy during or for at least six months following treatment. Female patients should use two forms of birth control during treatment and for 6 months following treatment. Males should use a condom and inform female partners of the need for a second form of contraception. Should you be released during the medication phase of your treatment it is extremely important that you establish a physician patient relationship with a specialist in the treatment of Hepatitis C. It is also important that you comply with the necessary life style changes to include not using illegal drugs or practicing unsafe sex.

DETERMINING ELIGIBILITY ☐ Not applicable. Patient admitted on treatment and eligibility verified.

☐ I consent to eligibility testing to include blood tests and x-ray studies as well as a liver biopsy. I understand that I may withdraw or cancel this consent in writing at any time.

PATIENT'S SIGNATURE	DATE SIGNED
PROVIDER'S SIGNATURE	DATE SIGNED

INITIATION/CONTINUATION OF MEDICATION TREATMENT

☐ I consent to medication treatment to include an interferon product and Ribavirin. I understand that I may withdraw or cancel this consent in writing at any time.

PATIENT'S SIGNATURE	DATE SIGNED
PROVIDER'S SIGNATURE	DATE SIGNED

DECLINE PARTICIPATION

☐ I decline evaluation or medication treatment at this time (circle one). I understand that I may request treatment in the future.

PATIENT'S SIGNATURE	DATE SIGNED
WITNESS' SIGNATURE	DATE SIGNED

Attachment D

HCV Evaluation & Referral Flow Sheet

PATIENT NAME	ID NUMBER	DATE	FACILITY

Step 1

Patient is positive for the Hepatitis C virus. (Quantitative HCV obtained.)

- ☐ Patient given Schering-Plough or Pegasys "Medication Guide," as appropriate.
- ☐ Provider educates patient on Hepatitis C infection and treatment. The education has been documented.

PROVIDER SIGNATURE:_____ **DATE:**_____

Step 2

Initiate eligibility process

- ☐ Patient signed Informed Consent or refusal for determining eligibility for Interferon/Ribavirin treatment.
- ☐ Obtain labs as required to determine eligibility. **(If no other absolute exclusion criteria are present.)**

PROVIDER SIGNATURE:_____ **DATE:**_____

Step 3

Absolute Exclusion Criteria*

- ☐ Age ≤ 18 or ≥ 60
- ☐ Remaining incarceration time ≤ 24 months.
- ☐ Presence of an Axis I diagnosis that is not controlled and stable as determined by the treating psychiatrist.
- ☐ History of solid organ transplant.
- ☐ Presence or history of an autoimmune disorder.
- ☐ Presence or history of decompensated cirrhosis, presence or history of ascites or encephalopathy (albumin ≤ 3.2 gm/dl, bilirubin > 3.0 gm/dl).
- ☐ CBC results outside acceptable limits (Hgb ≤ 12 females, ≤ 13 for males; WBC > 3,000; ANC ≤ 1,500 & platelets ≤ 100,000/mm).
- ☐ Creatinine ≥ 1.7 or creatinine clearance ≤ 50 ml/minute.
- ☐ Normal ALT (<2.0 times normal at 0, 3 and 6 months).
- ☐ Positive pregnancy test.
- ☐ Active TB
- ☐ Auto Immune Disease e.g. – Lupus, Graves Disease, R.A., M.S., Myasthenia Gravis
- ☐ Cancer – not in remission
- ☐ Hemoglobinopathies

* "No further evaluation should be completed **so long as the absolute criterion exists**."

Relative Exclusion Criteria**

- ☐ Hepatitis B Co-infection
- ☐ Diabetes – poorly controlled with Hgb. A1C ≥ 9.0
- ☐ Ischemic Cardiac Disease or Cerebrovascular Disease
- ☐ Hypertension – poorly controlled
- ☐ CHF
- ☐ Peripheral Vascular Disease – Symptomatic
- ☐ COPD – severe
- ☐ Seizures – poorly controlled
- ☐ Active Thyroid Disease
- ☐ Active Gout
- ☐ Significant CNS Trauma – recent within the past six months
- ☐ Poor adherence to treatment including ≤ 80% of clinic visits and medications, to the extent the inmate made the choices.
- ☐ Alcohol and illicit drug use within one year.
- ☐ Interferon/Ribavirin sensitivity.
- ☐ Life expectancy < 10 years.

**The provider is required to review relative exclusion criteria with the Regional Medical Director prior to proceeding with further evaluation.

Step 4

Non-Formulary Request for Genotype Testing

- ☐ Obtain HCV genotype. Provider submits Non-formulary Lab Request form with a copy of this form to the Regional Medical Director. Approval must be received prior to ordering tests.

STAFF SIGNATURE:_____ **DATE:**_____

Step 5

Risk Stratification and Treatment Options

- ☐ Provider reviews test results with patient to determine risk stratifications and therapeutic options.
- ☐ Provider submits an Outpatient RMD Consultation form for a liver biopsy, if indicated, with a copy of this form to the Regional Medical Director. Approval must be received prior to scheduling the biopsy.

PROVIDER SIGNATURE:_____ **DATE:**_____

Step 6

Initiation of Treatment

- ☐ Final eligibility determination completed. Liver biopsy results have been reviewed with the Regional Medical Director.
- ☐ Provider reviews Schering-Plough or Pegasys "Medication Guide" with the patient and provides education on Interferon/Ribavirin treatment.
- ☐ Patient signs informed consent for Interferon/Ribavirin treatment, a second time.
- ☐ Provider completes Formulary Exception Request form and orders medication treatment.

PROVIDER SIGNATURE:_____ **DATE:**_____

Step 7

Safety and Efficacy Monitoring

- ☐ Provider orders appropriate hematological and biochemical testing and viral load testing as required on the HCV treatment flow sheet. The provider addresses compliance at each visit and asks specific questions for depression and suicidal ideation.

PROVIDER SIGNATURE:_____ **DATE:**_____

EVIDENCE OF COMPENSATED CIRRHOSIS

Cirrhosis of the liver can be difficult to recognize if it is still in the early stages where the body is able to compensate for those biochemical and circulatory changes, which when advanced, become obvious to the caregiver. Some physical findings related to more advanced cirrhosis that can be picked up easily are jaundice, ascites, asterixis, mental status changes, telangiectasias, and caput medusae.

Certain laboratory studies can be helpful in diagnosing compensated cirrhosis. These are albumin and prothrombin time, CBC and platelets and LFTs including bilirubin. (Order a Diagnostic Profile 1 and Protime).

Results of a complete blood count can point towards cirrhosis as well. Thrombocytopenia, leukopenia and anemia can result from hypersplenism secondary to the portal hypertension of cirrhosis. Thrombocytopenia is the most common abnormality followed by leukopenia and then anemia. Neutropenia is the predominant finding related to leukopenia. Hypersplenism may result in any single abnormality or any combination of abnormalities. These low counts are caused by sequestration in the spleen. In the case of platelets, up to 90% of the total platelet mass can be found in the spleen. White cells and platelets seem to have approximately normal survival time in the spleen and in fact may be available if required in other areas of the body

Serum albumin and prothrombin time are dependent upon the synthetic capabilities of the liver which would be compromised if enough of the liver tissue is affected by scarring. Findings consistent with cirrhosis would be those of hypoalbuminemia and elevated INR.

Findings of normal to low AST and ALT can also be seen in cirrhosis. In the case of chronic hepatitis C one might expect to find elevated liver enzymes but because of the presence of cirrhotic tissue the amount of functioning liver tissue is reduced. This limits the number of normal hepatocytes that are able to leak enzymes that would normally result in the elevation of these serum levels. Additionally, it has been noted that in cirrhosis the ratio of AST to ALT can be greater than one. In chronic hepatitis C without cirrhosis this relationship is usually reversed.

Hyperbilirubinemia can be found in cirrhosis. Usually elevated total and direct bilirubin will be found but elevated indirect bilirubin can be found at times. Clinically apparent jaundice is ordinarily not evident until bilirubin levels reach about 3 mg/dl.

Patients with compensated cirrhosis should have an AFP and liver ultrasound prior to starting treatment for Hep C to screen for HCC (hepatocellular carcinoma).

Hypersplenism
Sudeep K. Aulakh, M.D., F.R.C.P.C., Ferri's Clinical Advisor 2003

Splenomegaly
Lewis Kaplan, MD FACS, Department of Surgery, Division of Trauma and Critical Care, Yale University School of Medicine on emedicine 2003

HEPATITIS C TREATMENT FLOW SHEET

Attachment F

Patient Name Last First	ID Number				Date of Birth ___ ___/___ ___/___ ___		Facility	
	Baseline	2 weeks	4 weeks	8 weeks	12 weeks	16 weeks	20 weeks	24 weeks
Date								
Vital Signs								
Blood Pressure								
Pulse								
Respirations								
Temperature								
Weight								
Laboratory Studies								
HCV RNA Quantitative[1]								
CBC w/diff								
Hgb[2]								
WBC[2]								
Platelets[2]								
Creatinine								
TSH[3]								
Pregnancy Test 2 ☐ NA								
HAV&HBV Dates(if applicable)	HAV	#1	#2	HBV	#1	#2	#3	
Mental Health Questions[2]								
Compliance Counseling[2]								
Provider Signature								

☐ Date treatment initiated:

☐ Treatment discontinued due to:

☐ Failed Response. ☐ Patient initiated. ☐ Contraindications.

Date: ___ ___/___ ___/___ ___ (mm/dd/yy) Reason: _____

☐ Date patient completed therapy: ___ ___/___ ___/___ ___ (mm/dd/yy)

1 Completed prior to initiation of therapy, at 12 weeks and 24 weeks following initiation of therapy, upon completion and 6 months following the completion of therapy. If there is not at least a 2-log decrease in HCV RNA at 12 weeks, treatment will be discontinued. If HCV RNA still shows measurable virus at 24 weeks, treatment will be discontinued.

2 Completed at each scheduled chronic care visit.

3 To be completed every three months during therapy and 6 months post end of treatment.

A copy of this form is to be submitted to the Regional Medical Director upon completion or discontinuation of therapy.

Attachment G

PEGLYATED INTERFERON AND RIBAVIRIN

DOSAGE

1. PegIntron (Alfa 2B)
   - 1.5 mcg/Kg/week

2. Ribavirin
   - (400mg BID dosing) (DOT)
   - 800 mg daily - genotype - 2 & 3
   - genotype 1a & 1b - >75 Kilo - 1200 mg daily
   - genotype 4 - <75 Kilo - 1000 mg daily

1. Pegasys (Alfa 2A)
   - 180 mcg weekly

2. Ribavirin
   - (400 mg BID dosing) (DOT)
   - 800 mg daily - genotype - 2 & 3
   - genotype 1a & 1b - >75 Kilo - 1200 mg daily
   - genotype 4 - <75 Kilo - 1000 mg daily
   - genotype 4 - >75 Kilo – 1200 mg daily

Ribavirin Dosage Modification Guidelines

Laboratory Values	Reduce Only Ribavirin Dose to 600 mg/day if:	Discontinue Ribavirin if:
Hemoglobin in patients with no cardiac disease	< 10 g/dL	< 8.5 g/dL
Hemoglobin in patients with history of stable cardiac disease	≤ 2 g/dL decrease in hemoglobin during any 4 week period treatment	< 12 g/dL despite 4 weeks at reduced dose

Hematological

Hematological Dose Modification Guidelines

Laboratory Values	Pegasys Dose Reduction	Discontinue Pegasys if:
ANC <1000/mm^3	135 µg	ANC <500/mm^3, treatment should be suspended until ANC values return to more than 1000/mm^3. Reinstitute at 90 µg and monitor ANC.
Platelet <100,000/mm^3	90 µg	Platelet count <25,000/mm^3.

Renal

In patients with end-stage renal disease requiring Renal Dialysis, dose reduction to 135 mcg of Pegasys is recommended. Patients with a creatine clearance of less than 50 cc/minute, Pegasys **should not** be used.

Dose Modification - Pegasys

General

When dose modification is required for moderate or severe adverse reactions, initial dose reduction to 135 mcg (0.75 ml) is generally adequate. However, in some cases, dose reduction to 90 mcg (0.5 ml) may be needed. Following improvement of the adverse reaction, re-escalation of the dose may be considered.

Guidelines for Dose Modification and Discontinuation of PEG-Intron or PEG Interferon/Ribavirin for Hematologic Toxicity

Laboratory Values		PEG-Intron	Rebetol
Hgb*	<10.0g/dl	.....	Decrease by 200mg/day
	<8.5g/dl	Permanently discontinue	Permanently discontinue
WBC	<1.5 x10^9/L	Reduce dose by 50%	.....
	<1.0 x10^9/L	Permanently discontinue	Permanently discontinue
Neutrophil	<0.75 x10^9/L	Reduce dose by 50%	.....
	<0.5 x 10^9/L	Permanently discontinue	Permanently discontinue
Platelets	<80 x10^9/L	Reduce dose by 50%	.....
	<50 x10^9/L	Permanently discontinue	Permanently discontinue

* For patients with a history of stable cardiac disease receiving PEG-Intron in combination Ribavirin, the PEG-Intron dose should be reduced by half and the Ribavirin dose by 200mg/day if a > 2g/dL decrease in hemoglobin is observed during any 4 week period. Both PEG-Intron and Ribavirin should be permanently discontinued if patients have hemoglobin level < than 12 g/dL after this Ribavirin dose reduction.

Recommended dose of Ribavirin (BID dosing) (given via DOT)

< 65 Kilo – 800mg daily
> 65 – 85 Kilo – 1000mg daily
> 85 Kilo – 1200mg daily
Genotype – non 1A & 1B
800mg daily

CLINICAL GUIDELINES FOR EVALUATION OF ALPHA FETO PROTEIN AND HEPTOCELLULAR CARCINOMA (HCC)

- ✓ After birth serum levels fall to the normal (below 20 ng/ml).
- ✓ Modest elevations (greater than 20) but seldom greater than 400 can occur in acute or chronic liver injury.
- ✓ In cirrhotic patients, a steady increase or levels greater than 500 ng/ml are indicative of HCC.
- ✓ Levels of 500 ng/ml indicate tumor size of 2-3 cm.
- ✓ Levels tend to stabilize in individual patients regardless of tumor size.
- ✓ AFP done routinely on all cirrhosis patients – monitor every six months.
- ✓ AST/ALT ratio – yearly.

Interferon – Ribavirin
Side Effects
Symptoms Prevention and Management

Fever, chills, and muscle and joint pains are frequently encountered with the start of interferon/ribavirin therapy. Symptoms generally begin between 2-12 hours after injection. The worst symptoms may occur during the first 3 injections, usually subside in severity within 1-2 months of therapy, but persist to some degree during the course of treatment. By administering the injections as late in the day as possible, the individual may sleep through the worst symptoms. Encouraging adequate fluid intake and rest may reduce symptom severity. Pre-treatment with the medications listed below can significantly reduce these side effects.

Acetaminophen, 500 mg tabs, 2 tablets with each Interferon injection. May repeat up to three times daily to reduce or relieve flu-like symptoms.

OR

Ibuprofen, 200 mg tabs, 2 tablets with each Interferon injection. May repeat up to three times daily to reduce or relieve flu-like symptoms.

Headache frequently accompanies other "flu-like" symptoms associated with Interferon injections. It is important to rule out other conditions. Assess neurological status, look for other causes: hydration status, migraine history, HTN, dental problems, allergies, other drug interactions, stress, sleep disturbances, hormonal changes, caffeine, anemia, need for new glasses. Therapy should be supportive in nature and address problems that can be corrected, such as limiting light and sound stimulation. Consider the use of NSAIDS, Fioricet, acetaminophen, or amitriptyline therapy.

Myalgia/neuralgia also frequently accompanies other "flu-like" symptoms associated with interferon injections. Encourage mild, low impact exercise and warm compresses to affected areas.

Fatigue is often associated with interferon injections and often persists to some degree throughout the course of therapy. These symptoms can be minimized by maintaining hydration, encouraging moderate exercise, energy conservation and maintaining good nutrition.

Nausea, vomiting and/or diarrhea can result from interferon/ribavirin therapy. Symptoms can become so severe that maintaining weight and nutritional status becomes a big challenge. Effects may be managed by encouraging frequent small meals, avoidance of acidic, spicy or greasy foods and providing nutritional supplements. Monitor electrolytes as needed. Anti-emetics and anti-diarrhea agents may need to be used.

Taste alterations specifically, complaint of metallic taste in the mouth is common with therapy. This can add to the anorexia experienced by patients during therapy. Advising the use of plastic utensils, drinking cranberry juice or lemonade and using hard candy mints, chocolate and citrus drinks may lessen severity.

Alopecia usually presents as a slow progression in severity over the course of therapy and is reversible with discontinuation of treatment. Encourage measures to diminish severity such as the use of mild

shampoos and conditioners. Stress avoidance of hair products that cause dryness and wearing constrictive head wear.

Cough may develop during therapy. Assess pulmonary status with PFT or CXR as indicated, rule out other causes such as allergies or asthma. Supportive therapies include increased fluid intake, use of a humidifier, avoidance of irritants such as smoke and aerosol sprays, and sucking on hard candy or cough drops.

Itching and rash can occur. Assess baseline skin condition; consider autoimmune conditions such as psoriasis. Monitor liver and renal functions tests. Symptoms can be minimized by encouraging use of mild soaps and wearing sunscreen when outside. If symptoms persist, consider OTC hydrocortisone cream and antihistamines.

Mood Disturbances, namely depression, anxiety, irritability and insomnia are common. interferon/ribavirin therapy tends to worsen pre-existing symptoms, and these problems need to be addressed and stabilized prior to beginning therapy.

SEVERE PSYCHIATRIC EVENTS HAVE OCCURRED WITH INTERFERON THERAPIES, INCLUDING DEPRESSION, PSYCHOSES, AGGRESSIVE BEHAVIOR, HALLUCINATIONS, VIOLENT BEHAVIOR, HOMICIDAL IDEATION, SUIDICAL IDEATION, ATTEMPTS AND SUICIDES IN PATIENTS WITH AND WITHOUT PREVIOUS PSYCHIATRIFC DISORDERS*

Hematology Concerns

Ribavirin Induced Hemolytic Anemia: Hemoglobin levels generally decrease from baseline within the first 4 weeks of combination therapy. A mean decrease between 2-3 g/dL is common. Hemoglobin levels usually stabilize after 4 weeks of therapy and return to pretreatment levels within 8 weeks of discontinuation. As levels decline, patients often complain of shortness of breath with any exertion, chest pain, weakness, fatigue and anorexia. People with pre-existing cardiovascular disease must be closely monitored. Dose reduction of ribavirin according to modification guidelines may be necessary and education and reassurance is important in preventing early termination.

Neutropenia commonly occurs with interferon therapy, is transient in nature and usually occurs within the first few weeks of initiation of therapy. It often lasts for the duration of therapy and recovery to baseline levels occurs upon cessation of treatment. Monitor labs according to protocol, and management involves dose reduction of interferon when ANC levels fall $<750/mm^3$.

Thrombocytopenia may be sudden and severe enough to discontinue therapy. Watch platelet counts carefully, and refer to dose reduction table if platelets drop below $50,000/mm^3$. Advise patients to report bruising, nosebleeds or petechiae.

Summary
National Institutes of Health
Consensus Development Conference Statement
Management of Hepatitis C
Final Statement

*The complete 44-page document can be found at http://www.nih.gov/.

The NIH Consensus Development Conference on Management of Hepatitis C: 2002 was held June 10 - 12, 2002. The final statement was published September 12, 2002. The "Final Statement" contains the following disclaimers:

1. "This statement is not a policy statement of the NIH or the Federal Government" and
2. "Thus, it provides a "snapshot in time" of the state of knowledge".

The Virus

The lack of a vigorous T-lymphocyte response and the high propensity of the virus to mutate appear to promote a high rate of chronic infection. The extensive genetic heterogeneity of Hepatitis C virus (HCV) has important diagnostic and clinical implications, perhaps explaining difficulties in vaccine development and the lack of response to therapy. Genotype 1 accounts for 70 to 75 percent of all HCV infections in the United States and is associated with a lower rate of response to treatment.

HCV replicates preferentially in hepatocytes but is not directly cytopathic. During chronic infection, HCV RNA reaches high levels, generally ranging from 10^5 to 10^7 international units (IU)/mL, but the levels can fluctuate widely. However, within the same individual, RNA levels are usually relatively stable.

Epidemiology

Although difficult to assess accurately, the incidence of HCV infections declined sharply in the late 1980s. However, the estimated prevalence of HCV in the U.S. is at least 1.8 percent of the population and a fourfold increase in the number of adults diagnosed with chronic HCV infection is projected from 1990 to 2015. Currently, persons aged 40 to 59 years have the highest prevalence of HCV infection, and in this age group, the prevalence is highest in African Americans (6.1%). High HCV seroprevalence rates (from 15-50 percent) have occurred in specific subpopulation, such as homeless, incarcerated persons, injection drug users, and persons with hemophilia who were treated with clotting factors before 1992. The highest seroprevalence rates (70 to more than 90 percent) have been reported in the last of these two groups

Chronic Infection

Persistence of HCV infection is diagnosed by the detection of HCV RNA in the blood for at least 6 months. In general, prospective studies have shown that 60 to 85 percent of HCV-infected persons develop chronic infection.

The most important sequelae of chronic HCV infection are progressive liver fibrosis leading to cirrhosis, end-stage liver disease, and Hepatocellular Carcinoma (HCC). Estimates of the proportion of chronically infected persons who develop cirrhosis 20 years after initial infection vary widely from 2 to 4 percent in studies of children and young women to as high as 20 to 30 percent in middle-aged transfused subjects. The actual risk is likely intermediate between these two ranges, on the order of 10 to 15 percent. There is little evidence that virologic factors, including viral load, viral genotype, and quasi-species diversity significantly affect the risk of progression of liver disease. However, many host factors increase this risk, including:

- Older age at time of infection,
- Male gender,
- Immunosuppression such as that associated with HIV infection, and
- Concurrent chronic hepatitis B infection.
- Higher levels of alcohol use play an important role in promoting the development of progressive liver disease, with strong evidence for the detrimental effects of 30 g/day in men (~ equivalent to 2 beers, 2 glasses of wine, or 2 mixed drinks) and 20 g/day in women.
- Conversely, individuals infected at a younger age have little or no disease progression over several decades.

Hepatocellular Carcinoma

HCC rarely occurs in the absence of cirrhosis or advanced fibrosis. Risk factors for HCC in persons with chronic HCV infection are largely the same as those for the development of decompensated cirrhosis. Some but not all studies suggest that treatment with interferon and ribavirin may reduce the risk of developing HCC in HCV patients with cirrhosis, but more data are needed.

HCV Serologic Assays

Enzyme immunoassay (EIA) tests are reproducible, inexpensive, and FDA-approved for use in the diagnosis of HCV infection. The very high sensitivity (low rate of false negative) and specificity (low rate of false positive) of the version 3 (third-generation) EIAs (sensitivity of greater than 99 percent, specificity of 99 percent in immunocompetent patients) obviate the need for a confirmatory immunoblot assay in the diagnosis of individual patients with clinical liver disease, particularly those with risk factors for HCV infection.

Qualitative HCV RNA Assays

Chronic HCV infection in a patient with a positive EIA test should be confirmed by a qualitative HCV RNA assay with a lower limit of detection of 50 IU/mL or less (approximately 100 viral genes/mL). A single positive qualitative assay for HCV RNA

confirms active HCV replication, but a single negative assay does not exclude viremia and may reflect only a transient decline in viral level below the level of detection of the assay.

Until future studies determine whether the sustained virological response (SVR) will be sustained over the long term following successful antiviral treatment, periodic measurements of HCV RNA may need to be performed.

Quantitative HCV RNA Assays

Testing for HCV RNA level (or viral load) with a quantitative assay provides accurate information on HCV viral levels. Significant variability exists between available assays. The clinical utility of serial HCV viral levels in a patient is predicated on continued use of the same specific quantitative assay that was used in the initial determination of the viral level. While there is little correlation between disease severity or disease progression with the absolute level of HCV RNA, quantitative determination of the HCV level provides important information on the likelihood of response to treatment in patients undergoing antiviral therapy.

ALT

Testing for serum ALT levels is the most inexpensive and noninvasive, but relatively insensitive, means of assessing disease activity. Serial determinations of ALT levels over time may provide a better means of assessing liver injury, but the accuracy of this approach has not been well documented. Patients who initially have a normal ALT level should undergo serial measurements over several months to confirm the persistence of normal ALT levels. Although loss or reduction in HCV RNA is the primary indicator of response to antiviral therapy, the resolution of elevated ALT levels with antiviral therapy appears to be an important indicator of disease response.

Noninvasive Tests of Fibrosis

No single test or panel of serologic markers can provide an accurate assessment of intermediate stages of hepatic fibrosis. Similarly, quantitative tests of liver function and radiologic imaging of the liver are sensitive for diagnosing advanced cirrhosis but are not useful in assessing hepatic fibrosis and early cirrhosis.

Liver Biopsy

Liver biopsy provides a unique source of information on fibrosis and assessment of histology. The information obtained on liver biopsy allows affected individuals to make more informed choices about the initiation or postponement of antiviral treatment. Thus, the liver biopsy is a useful part of the informed consent process.

In general, a baseline assessment of liver histology offers a valuable standard for subsequent comparisons. However, the appropriate interval for subsequent evaluations is yet to be determined.