Chapter

69

Hepatitis C — Progress in Management

SAMIR R SHAH

Hepatitis C is one of the leading causes of chronic liver disease and its sequel worldwide. Despite legislation for compulsory testing of blood donors for Hepatitis C virus starting from 1992 onwards, the burden of end stage chronic liver disease due to HCV will actually increase over the next decade. This is due to the slow progression of the liver diseases over 20-30 years and patients infected by untested blood in the past presenting later with chronic liver disease and those untreated or not responding to treatment gradually deteriorating over the years and requiring liver transplantation. Effective treatment is available and long list of newer drugs are undergoing clinical trials. However, in our country only small proportion are identified or present early enough for the treatment to be most effective. Early identification and awareness of the availability of appropriate treatment is crucial.

Identifying Population at Risk

Hepatitis C virus infection remains asymptomatic and mildly elevated transaminases may the only presentation. Symptoms if at all would be mild and seemingly nonspecific like fatigue and feeling unwell. Abnormal AST/ALT if persistently elevated would signify ongoing liver disease. In this group, a silent hepatitis C virus infection should be suspected, if there is a history of blood transfusion in the past or no other obvious etiological factors for liver disease identified. Transmission of virus between spouses and vertical transmission from mother to child of the patients with hepatitis C virus are at much smaller risk (<5%), compared to other infections like HBV and HIV. Patients undergoing hemodialysis are also exposed to hepatitis C virus during the dialysis. Unfortunately, there is no vaccine to protect these patients like with hepatitis B virus. In chronic renal failure, AST/ALT may be normal and yet there may be ongoing liver injury. In presence of HIV co-infection the risk of transmission is much higher as is the case with IV drug addicts and men who have sex with men. Commonest cause for hepatitis C virus infection is a history of blood transfusion prior to the time when a mandatory testing for hepatitis C virus has been made applicable. Hence, it may be appropriate to test all patients who have past history of multiple blood transfusions especially the high risk groups like hemophiliacs and thalassemics and more so if they also have abnormal liver enzymes in addition.

Assessment for Treatment

Evaluation of the Virological Status in Anti-HCV

Currently available third generation enzyme immune assays (EIA) for Antibody to Hepatitis C Virus (Anti HCV) are highly sensitive in immunocompetent patients.

No further confirmatory test is necessary for diagnosis in Anti-HCV positive patients if there are high risk factors or evident liver disease but HCVRNA and Genotyping may be done before starting treatment for further quantifying the amount of virus and the Genotype. Treatment responses are different amongst the different genotypes. Genotype I does not have as good a response genotype II-III.

Patients who are immunocompromised, or on hemodialysis may have false negative Anti-HCV test due to poor antibody response. HCVRNA is necessary in those situations to confirm the presence of the virus.

In the event of a positive Anti-HCV test in a blood donor, confirmation of the presence of virus is required as Elisa test is highly sensitive with a lower specificity in this setting and a likelihood of a false-positive test raising anxiety and concern to the blood donor. HCVRNA testing would be required in this situation to confirm or rule out HCV infection and not surprisingly, HCVRNA may be negative in a significant proportion of this group.

Assessment of Liver Dysfunction

AST/ALT values if abnormal would suggest necroinflammation however, the level may be normal at the time of testing and only cyclically abnormal. Concerns have been raised recently regarding the limits of normal value of AST/ALT. Patients who have seemingly normal values have been noted to have underlying significant liver disease including fibrosis on a liver biopsy. Such patients when treated show a response with further lowering of their ALT values signifying that seemingly normal values were actually high and may be even up to 2 times baseline value and yet not be above the upper limit of normal.

Liver biopsy helps in assessment of severity of the liver disease as the grade of inflammation and stage of fibrosis are not indicated by the value of AST/ALT. It is especially of importance in decision-making treatment if the AST/ALT values are normal or mildly abnormal. Non-invasive blood tests as markers of liver fibrosis and inflammation (Fibro test and Actitest) and new modality of scanner (Fibro scan) have been validated as alternatives to a liver biopsy and probably would replace it in the future for routine testing and follow up.

Specific Issues in Pretreatment Evaluation

1. **Hematological evaluation**: Estimation of WBC, Platelet count and Hb is necessary prior to initiation of Interferon and Ribavarin treatment as adequate levels are mandatory pre-treatment in anticipation of a fall during therapy (Table 1)
2. **Estimation of ANA** and **thyroid functions:** Interferon induces and exacerbates autoimmune disorders. The most common is risk of thyroiditis which is more when there is preexisting disease. ANA positivity does not preclude treatment but should lead to heightened attention towards autoimmune disorders and care during treatment.
3. **Psychiatric Evaluation:** 20% may develop depression during the treatment. Severe psychiatric symptoms are a contraindications for interferon treatment.
4. T**esting for HBsAg and HIV co-infection** as there are specific issues for treatment especially in HCV and HIV co-infection regarding the timing of treatment (CD4 count > 200 and avoidance of certain drugs like DDI and AZT).
5. **Pregnancy:** Interferon is contraindicated in pregnancy and manufacturers' advise contraception during treatment in view of the potential teratogenic effects.

Table 1: Indications for treatment

Should be treated	*Treatment may be individualized*	*Treatment contraindicated*
Chronic hepatitis C **With** Abnormal ALT **With** Liver biopsy showing significant inflammation and fibrosis **With** Compensated liver Disease	1. Acute hepatitis C not resolving within 3 months 2. Chronic Hepatitis C with Normal ALT and AST but with significant inflammation and fibrosis on Liver Biopsy 3. Active substance abuse	Decompensated liver disease Post renal transplant < 3 years of age Associated 1. Severe comorbid illness 2. Psychiatric illness 3. Autoimmune conditions 4. Pregnancy

TREATMENT

Over the last two decades sustained viral response to treatment have steadily increased from 6% with monotherapy with conventional interferon to 76-82% with Pegylated IFN and Ribavarin combination in Genotype-II-III. Combination therapy with Conventional/ Pegylated interferon dosage and Ribavarin is the standard of care now for treatment of chronic hepatitis C.

Interferon – are a family of pleotropic cytokines with antiviral, anti-proliferative and immunomodulatory properties. Pegylated interferon (PEGIFN) is a polyethylene glycol molecule conjugated to conventional interferon (Alfa 2a/2b). Pegylation increases the half life of interferon, reduces the volume of distribution and thereby produces sustained levels of IFN over longer duration. Availability of PEG IFN has resulted in a significant advantage over conventional interferon with improved response rates in genotype 1 and convenience of once a week dosing with no significant increase in

side-effects. However the disadvantage is of a higher cost of treatment. Conventional interferon are given in the dose of 3 million units subcut 3 times a week µg. Pegylated Interferon dosage are weight based in Peg IFN2B (1.0-1.5 mg/kg) and a standard dose of 180 mg in Peg IFN2A.

Ribavarin - A nucleoside analogue is a weak antiviral when used alone but in combination with Interferon, Ribavarin helps to reduce relapse rate. It is administered orally and excreted by renal route. Dosage of Ribavirin is crucial in difficult to treat patients like those Genotype I.

Treatment Variation According to Genotype - In Genotype I, Pegylated IFN is the preferred type as response rates are significantly better than the conventional type 46% v/s 25%. The duration of treatment in genotype-I, needs to be extended to 48 weeks with the dose of Ribavirin maintained at 1000 mg/day if body weight < 75 kgs and 1200 mg/day if > 75 kgs.

In Genotype II and III, response rates are much better and in the range of 75-82% and not significantly different with both conventional and Pegylated IFN. Ribavirin doses may be modest at 800 mg/day and duration of treatment may be shortened to 24 weeks. Recent data suggests that it would be possible to consider reducing the treatment duration still further to 12 weeks in a select group of genotype 2/3 patients with low viral load to begin with and early viral response at 4 weeks.

MONITORING DURING TREATMENT

Monitoring of Side Effects

Minor side effects are common and include headache and fatigue (51%), pyrexia (35%), insomnia (20%), alopecia (23%) depression (19%) and thyroid function abnormality. Monitoring for cytopenias and dose modification are recommended (Table 2) leading at times to discontinuation of therapy. In recent years with the use of erythropoietin (30,000 units once a week) and Granulocyte stimulating factors, treatment interruptions have become less frequent.

Patients with mild depression can be managed by SSRI group of antidepressants but those with symptoms of major depression may need help of psychiatrist and occasionally discontinuation of therapy.

ASSESSMENT OF RESPONSE AT THE END OF TREATMENT

Success of the treatment is assessed by sustained viral response (SVR) defined as absence of detectable HCV RNA in the serum six months following end of treatment.

Those who attain SVR have relapse rates less than 1% at 2-4 years. It is associated with normalization of SGPT and SGOT. Anti-HCV does not become negative with the treatment and is not the criterion for successful treatment.

SPECIAL SITUATIONS

1. **Acute HCV infection –** Acute-HCV is most often asymptomatic and presents as hepatitis in only a small percentage. Anti-HCV may not be positive early in the illness and diagnosis is confirmed by a HCVRNA positive test. Currently treatment may is advocated to persons who are exposed to Hepatitis C virus and who have HCVRNA positive 3 months after the acute infection.
2. **Patients with chronic renal failure –** These patients may get exposed to Heaptitis C Virus during hemodialysis and develop hepatitis. They do not tolerate treatment well and have high chances of Ribavirin induced hemolysis and anemia hence Ribavirin is to be avoided or used with caution in these patients. PEG IFN if used should be given at reduced doses. It is important to treat patients with CRF before a renal transplant, as treatment post-transplant is not advisable in view of possibility of

Table 2

Recommended dosage modification

WBC (Abs Neut)/mm^3		Platelets/mm^3		Hb gms%	
>75	Continue IFN	>50,000	Continue IFN	>10	Continue IFN
749-500	↓ dose IFN	>25-50,000	↓ dose IFN	8.5-10	↓ dose Ribavirin
499-250	Hold IFN	<25,000	Stop IFN	<8.5	Stop Ribavirin
<250	Stop IFN				

rejection due to the immunomodulatory action of interferon.

3. **Patients of chronic hepatitis C and normal SGOT/ SGPT –** Treatment may not be recommended in this group however decision may be individualized and considered if liver biopsy shows significant fibrosis. Safety and efficacy of treatment is similar to those with elevated SGPT.
4. **Treatment of hepatitis C in HIV co-infected -** Peg IFN and Ribavirin combination is the preferred therapy and large multicentre trials have confirmed its safety and efficacy. Choice of concomitant ART need to be considered. DDI should be avoided with Ribavirin due to likelihood of lactic acidosis and pancreatitis. AZT should be used with caution due to increased risk of anemia.

   Response rates earlier were much lower in the co-infected group as compared to the mono infected group with high rates of dropouts as a result of side effects. However with appropriate use of erythropoietin and granulocyte colony stimulating factors, patients are now able to maintain their Hb and WBC levels. Recent experience has suggested similar response rates reaching those noted in monoinfected patients.
5. **Treatment of non-responders and relapsers:** Those who have not responded or relapsed after a partial response are a difficult group to treat with no simple treatment options. Retreatment with optimized dose of Ribavirin or changing the type of interferon have resulted in some success as is combination with other agents like Thymosin Alpha.
6. **Liver transplantation:** Hepatitis C is one of the most common indication for liver transplantation and the only recommended treatment in decompensated liver disease. Strategies for prevention of HCV recurrence after transplant are inadequate and HCV recurrence in the new liver after the surgery is universal. However fortunately severe disease in the immediate postoperative period (Fibrosing cholestatic hepatitis) is uncommon (10-15%). Monitoring postoperatively with serial liver biopsies is recommended and appropriate treatment can be given postoperatively if HCV recurrence is associated with significant disease on histology in the new liver.

NEWER DRUGS IN THE HORIZON

With the limitation of currently available treatments, newer agents have been looked into the past few years and many more are under development. These drugs are specifically targeted to interfere with certain viral enzymes in the life cycle of HCV like protease and polymerase. Over the next decade, a long list of agents will be undergoing clinical trials. Some of these are already into phase II studies. The early experiences with these oral drugs do suggest an efficacy however, rapid development of resistance is also noted when used as a monotherapy. If they are combined with pegylated interferon the results in short term trials look promising.

The future is to look out for a right combination of different, oral, specifically targeted drugs acting against different phases of the replication cycle of hepatitis C, which would result in heightened and sustained efficacy without developing resistance.

SUGGESTED READING

1. Emmet B Keeffe. Hepatitis C Virus, Clinics in Liver Disease, 2005;9(3).
2. Hepatology, 25th Anniversary Issue, 2006;43(No 2, Suppl 1).
3. National Institute of Health Consensus Development Conference, Management of Hepatitis C: 2002. Hepatology, 2002;36(No.5 Suppl 1).
4. Paul d Berk, et al. HCV: New Paradigms, Seminars in Liver Disease 2005;25(1).
5. Shiv K Sarin, Kunio Okuda (Eds). Hepatitis B and C, Carrier to Cancer, Harcourt India Pvt. Ltd, New Delhi 2002.