INTRODUCTION

Hepatitis C virus (HCV) a member of the Flaviviridae family, was first identified in 1979, as a blood borne infection which can infect the liver decades before symptoms appear. It is estimated that 3% of the world population are chronically infected with HCV but most of them have no knowledge about the infection and its hepatic consequences. HCV infection can cause chronic hepatitis which can result in serious long term consequences including cirrhosis, hepatocellular cancer (HCC), liver failure and need for transplantation. Six HCV genotypes, numbered 1–6, and a large number of subtypes have been described. The standard of care (SOC) therapy for patients with chronic hepatitis C virus (HCV) infection has been the use of both peginterferon (PegIFN) alpha 2a or 2b and ribavirin (RBV). In patients with HCV genotypes 1, 4, 5, and 6, these drugs are administered for 48 weeks whereas for HCV genotypes 2 and 3, treatment duration is 24 weeks. The goal of treatment for chronic HCV infection is to achieve sustained virologic response (SVR), defined as undetectable HCV RNA levels 6 months after completing treatment. Attaining SVR has been shown to slow disease progression, and to reduce mortality associated with HCV infection. The chance of inducing SVR is 40%-50% in those with genotype 1 and of 80% or more in those with genotypes 2 and 3 infections. Since half of patients with genotype 1 do not achieve SVR with SOC therapy, alternative treatments continue to be tested. The two protease inhibitors (PI), telaprevir (TVR) and boceprevir (BOC) are the direct acting antiviral agents (DAA) licensed for use in HCV Geno 1 infection. The role of physician is crucial in identifying population at risk with early diagnosis and guidance for appropriate management.

Identifying Population at Risk: HCV infection remains asymptomatic and mildly elevated transaminases may be 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, if no other obvious etiological factors for liver disease are identified a silent hepatitis C virus infection should be suspected especially if there is a history of blood transfusion. 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 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. In India Anti HCV testing became mandatory only after 2002 and any blood transfusion before this could be a risk factor for HCV transmission. Hence, it may be appropriate to test all patients who have a past history of multiple blood transfusions especially the high risk groups like hemophiliacs and thalassaemias and more so if they also have abnormal liver enzymes in addition.

TOOLS FOR DIAGNOSIS, ASSESSMENT OF DISEASE SEVERITY, MONITORING TREATMENT

a. Evaluation of the Virological Status. Diagnosis of chronic HCV infection is based on the presence of both anti-HCV antibodies, detected by third generation enzyme immune assays (EIA) and HCV detected by molecular assays. The most recent assays are based on real- time polymerase
Non invasive blood tests as markers of liver fibrosis

Liver biopsy helps in assessment of severity of liver disease

In the event of a positive Anti HCV test in a of blood do-

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

In the event of a positive Anti HCV test in a of blood don-
or, 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. HCV RNA testing would be required in this situation to confirm or rule out HCV infection and not surprisingly, HCV RNA may be negative in a significant proportion of this group.

Assessment of severity of liver disease: 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. Liver biopsy may reveal advanced fibrosis or cirrhosis that necessitates surveillance for hepatocellular carcinoma (HCC) and/or screening for varices. It has been widely regarded as gold standard for defining liver disease status but it has drawbacks such as risk due to invasive procedure, sampling error and requirement for special expertise to interpret the histopathology.

‘Non invasive blood tests as markers of liver fibrosis and inflammation (Fibro test and Actitest) and new modality of scanners have been developed and extensively evaluated in patients with chronic HCV. Transient elastography (Fibroscan and Acoustic Radiation Frequency Imaging A.R.F.I.) uses ultrasound and low frequency elastic waves to measure liver elasticity. Although increasingly popular currently this method still has limitations and liver biopsy remains gold standard. Both non-invasive methods have been shown to accurately identify only patients with mild fibrosis or cirrhosis. They are less able to discriminate moderate and severe fibrosis.

Role of IL28B Testing:

Genome wide association studies have demonstrated a host polymorphism in a nucleotide sequence located on chromosome 19 near the IL28B (Interferon lambda 3) gene. The CC genotype is favourably associated with higher rates of sustained viral response and spontaneous clearance of HCV infection compared to those with CT and TT genotypes.

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 2)

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 untreated or uncontrolled psychiatric disorders are contraindications for interferon treatment.

4. Testing 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 of Ribavirin.

Treatment: The goal of therapy is to eradicate HCV infection and thereby prevent complications and death from HCV infection. Identifying individuals at risk for developing
Advances in Management of Hepatitis C

Progressive disease is difficult. Table 1 summarises indications and contra-indications to start antiviral therapy for HCV infection.

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 Ribavirin combination in Genotype-II-III. Combination therapy with Pegylated interferon and Ribavirin is the recommended standard of care now for treatment of chronic hepatitis C. However conventional interferons are as effective and a considerably cheaper option in easier to treat Genotype 3.

**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 is given in the dose of 3 million units subcut 3 times a week. Pegylated Interferon dosage are weight based in Peg IFN2B (1.0-1.5mg/kg) and a standard dose of 180ug in PegIFN2A.

**Ribavirin** - A nucleoside analogue is a weak antiviral when used alone but in combination with Interferon, Ribavirin helps to reduce relapse rate. It is administered orally and excreted by renal route. Dosage of Ribavirin is crucial in difficult to treat patients with genotype 1 and 4.

**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 1000mg/day if body weight <75kgs and 1200mg/day if >75kgs. 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 800mg/day and standard duration of treatment is 24 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 to 40000 units once a week) and Granulocyte stimulating factors, treatment interruptions have become less frequent in difficult to treat cirrhotic patients.

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**Table 1: Indications for treatment**

<table>
<thead>
<tr>
<th>Should be treated</th>
<th>Treatment may be individualized</th>
<th>Treatment contraindicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic hepatitis C and Abnormal ALT</td>
<td>1. Acute hepatitis C not resolving within 3 months</td>
<td>Decompensated liver disease Child C</td>
</tr>
<tr>
<td>with Liver biopsy showing significant inflammation and fibrosis.</td>
<td>2. Chronic Hepatitis C with Normal ALT and AST but with significant inflammation and fibrosis on Liver Biopsy &lt; 2 years of age</td>
<td>Post solid organ transplant (renal, heart, lung)</td>
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<tr>
<td>Compensated Liver Disease</td>
<td>3. Active substance abuse</td>
<td>Associated:</td>
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<tr>
<td></td>
<td></td>
<td>1. Severe co morbid illness</td>
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<tr>
<td></td>
<td></td>
<td>2. Psychiatric illness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Auto Immune Conditions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Untreated thyroid disease</td>
</tr>
</tbody>
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**Table 2: Recommended Dosage Modification**

<table>
<thead>
<tr>
<th>WBC (Abs Neut)/mm³</th>
<th>Platelets/mm³</th>
<th>Hb (gms%)</th>
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<tbody>
<tr>
<td>&gt; 750 Continue IFN</td>
<td>&gt;50,000 Continue IFN</td>
<td>&gt;10 continue IFN</td>
</tr>
<tr>
<td>749-500 ↓ dose IFN</td>
<td>&gt;25-50,000 ↓ dose IFN</td>
<td>8.5-10 dose of Ribavarin</td>
</tr>
<tr>
<td>499-250 Hold IFN</td>
<td>&lt; 25,000 Stop IFN</td>
<td>&lt; 8.5 Stop Ribavarin</td>
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<tr>
<td>&lt;250 Stop IFN</td>
<td></td>
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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 SVR – defined as absence of detectable HCV RNA in the serum six months following end of treatment. Intermediate endpoints are used during SOC treatment to assess the likelihood of an SVR and tailor duration of therapy. They include HCV RNA levels at 4, 12 and 24 weeks; these are interpreted in comparison to baseline HCV RNA level.

Those who attain SVR have long term clearance of the virus with relapse rates less than 2%. Anti HCV does not become negative with the treatment and is not the criterion for successful treatment.

**PREDICTORS OF SVR**

i. HCV genotype

ii. Genetic polymorphisms located in chromosome 19 (IL28B), particularly in genotype 1 patients

iii. Stage of liver fibrosis (absence of bridging fibrosis or cirrhosis)

iv. Elevated ALT (>3 X ULN)

v. Female, age < 40 yrs

vi. Non African-American race

vii. Absence of insulin resistance/Steatosis on liver biopsy

viii. Lower body weight(<=75 kg)

**Relapsers**: are defined as patients who achieved undetectable HCV RNA at the end of treatment and subsequently relapsed and did not achieve SVR. Patients relapsing after treatment with standard IFN-based regimens respond to re-treatment with pegylated IFN-alpha and ribavirin in 32-53% of cases

**Non-responders**: are patients who failed to achieve a decline of 2 log HCV RNA IU/ml after 12 weeks of treatment or who never achieved undetectable HCV RNA during treatment of 24 weeks

**SPECIAL SITUATIONS**

1. **Acute HCV infection** – Acute HCV is most often asymptomatic (50-90%) 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 HCV RNA positive test. 55-85% cases fail to eradicate the infection spontaneously. Spontaneous resolution is more common among those with IL28B CC, infants and young women compared to older patients. Currently treatment is advocated to persons who are exposed to Hepatitis C virus and who have HCV RNA positive 3 months after the acute infection. PegIFN-alpha monotherapy (PegIFN 2a, 180 mcg/week or PegIFN2b, 1.5 mcg/week) for 24 weeks is recommended in patients with acute hepatitis C and this has shown viral eradication in 90% of patients. Patients who fail to respond should be re-treated using SOC therapy for chronic hepatitis C.

2. **Patients with chronic renal failure** – These patients may get exposed to HCV infection during hemodialysis and develop hepatitis. They do not tolerate treatment well and have high chances of ribavirin induced hemolysis and anemia, also ribavirin is cleared by the kidneys, hence ribavirin is to be avoided or used with extreme caution in these patients. PEG IFN monotherapy if used should be given at reduced doses. SVR rates are substantially lower than in non-dialysis patients. It is important to treat patients with CRF before a renal transplant, as treatment post transplant is not advisable in view of possibility of rejection due to the immunomodulatory action of interferon.

3. **Patients of Chronic Hepatitis C and normal SGOT/ SGPT** – There have been two issues in this group of patients. One is what constitutes a normal ALT and second is whether patients with normal ALT warrant treatment. Recent data, Prati criteria, suggest that ULN for ALT should be 30 IU/L for men and 19 IU/L for women. Treatment may not be recommended in this group however decision may be individualized and based on age, severity of liver disease assessed by liver biopsy, potential for side-effects, likelihood of response and presence of co-morbid conditions. Safety, efficacy as well as treatment regimen is similar to those with elevated SGPT.

4. **Diagnosis and Treatment of HCV in children**:

Routine testing of anti-HCV at birth of children born to HCV-infected mothers is not recommended due to passive transfer of these antibodies from mother. This test should be performed at 18 months of age. Testing for HCV RNA can be considered at 1-2 months of age. Children aged 2-17 years, infected with HCV should be considered for treatment using the same criteria as that for adults. The PegIFN alpha-2b is used at 60 mcg/week in combination with ribavirin, 15 mg/kg for 48 weeks.

5. **Treatment of Hepatitis C in HIV Co-infected** – Indications for HCV treatment are identical to those in patients with monoinfection. Peg IFN and Ribavirin combination is the preferred therapy and large multicentre trials have confirmed its safety and efficacy, however dose of ribavirin (15 mg/kg) should always be weight-based, irrespective of genotype. Choice of concomitant HAART need to be considered, as progression of
liver disease is accelerated in patients with HIV-HCV co-infection. Also if CD4 count is below 200 cells/microlit, then this should be improved using HAART prior to commencing anti-HCV treatment. 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 drop outs 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.

6. HBV coinfection: Patients with HCV-HBV co-infection, HCV appears to be the main cause of chronic hepatitis whilst HBV DNA levels are low or fluctuate considerably. It is important to exclude hepatitis delta virus (HDV) infection. Indications of anti-HCV treatment as well as treatment regimens using SOC therapy is similar as mono-infected patients. SVR rates are comparable as well as treatment regimen using SOC therapy is similar compared to HCV mono-infected patients. Telbivudine has increased risk of neurotoxicity when used with IFN.

7. Treatment of non responders and Relapsers: Those who have not responded or relapsed after treatment are a difficult group to treat with no simple treatment options. Treatment with longer duration and optimized dose of Ribavirin or changing the type of interferon has resulted in only partial success. Treatment with PegIFN and ribavirin can be considered for non-responders or relapsers who have previously been treated with non-Peg IFN with or without RBV or with PegIFN monotherapy. In Geno 1 relapers and non responders addition of the new D.A.A. Telaprevir and Bocepravir have shown substantial increase in response rates. Unfortunately for Geno 3 which is the prevalent genotype in India there is no new D.A.A. licensed for use in nonresponder or relapsed patients.

8. Treatment of Patients with compensated and decompensated cirrhosis: Patients with compensated cirrhosis due to HCV can be treated with SOC therapy but will require close monitoring for side-effects. Patients with HCV-related decompensated cirrhosis should be referred for consideration of liver transplantation before an attempt to treat with anti-viral therapy. In those with HCV genotype 2 and 3 with cirrhosis, CTP class B treatment seems appropriate with lower dose of PegIFN and RBV and careful use of growth factors to support treatment associated anaemia and leucopenia. Patients with genotype 1 the response rate is extremely low (7% compared to 44% in genotype 2 and 3) in patients with decompensated HCV cirrhosis and may not be justified for treatment. Child C decompensated cirrhotics should not be treated with interferon and should undergo liver transplant. Antiviral treatment can safely be done post transplant in the eventuality of recurrence of HCV infection.

9. 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 post-operative period (Fibrosing cholestatic hepatitis) is uncommon (10-15%). Monitoring post operatively with serial liver biopsies is recommended and appropriate treatment can be given post operatively 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, particularly the direct-acting agents (DAA) 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 under going clinical trials. Some of these are already in phase III studies (Combination of Peg IFN, RBV and HCV protease inhibitor). The DAA inhibit the HCV nonstructural protein (NS3/4A) serine protease and have been approved by Food and drug administration (FDA) in mid 2011. Both DAA, Boceprevir (BOC) and telaprevir (TVR) have shown potent inhibition of HCV genotype 1 replication and improvement in SVR rates in treatment naïve and treatment experienced patients. The early experiences with these oral drugs do suggest an efficacy however, potential challenges should be considered including rapid development of resistance with monotherapy and additional side-effects, drug-drug interactions associated with protease inhibitors. In the BOC trials, anaemia and dysgeusia were the most common side-effects whereas in the TVR trials, rash, anaemia, pruritus, nausea and diarrhea were more frequently encountered compared to SOC alone. DAA have shown interaction with statins, immunosuppressants and drugs used to treat HIV co-infections. Advanced fibrosis and African-American ethnicity has been identified being as negative predictor for response. Besides DAA, other drugs such NS5A and NS5B
polymerase inhibitors, cyclophilin inhibitors, new forms of IFN, derivatives of RBV and therapeutic vaccines are being studied in various trials.

Anti-HCV therapy has evolved from 2001 to 2011 with great promise now especially in difficult to treat genotype 1 patients. The future being looked up to is a combination of oral agents without any need for Interferon. The standard treatment of Interferon and Ribavirin is freely available in India. However the numbers of patient who have access to a benefit from this treatment are still small. Physicians need to focus their attention on prevention, early detection and appropriate referral for the available treatment.

REFERENCES


Recommended Reading

2. EASI Clinical Practice Guidelines: Management of hepatitis C virus infection