Brief Communication

Hepatitis C - Goals of therapy and monitoring of therapy

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Background and magnitude of the problem

The hepatitis C virus (HCV) is a major public health problem and a leading cause of chronic liver disease[1]. An estimated 180 million people are infected worldwide [2]. The primary route of transmission of HCV is through exposure to infected blood. Transmission risk factors include injection drug use, blood transfusion, solid organ transplantation from infected donors, unsafe medical practices, occupational exposure to infected blood, birth to an infected mother, multiple heterosexual partners, and high-risk sexual practices[3-7]. High HCV seroprevalence rates (from 15 to 50 percent) have been observed in specific subpopulations, such as the homeless, incarcerated persons, veterans being followed at Veterans Affairs Medical Centers, and hemophiliacs, with the highest rates (70 percent to 90 percent) reported in injection drug users. In the general population, persons aged 40 to 59 years have the highest prevalence of HCV infection. Because of the high rate of persistent infection long-term complications of chronic HCV infection are projected to increase in next few years.

Acute hepatitis C leads to chronic infection in approximately 75 percent of cases. Age at the time of infection appears to be an important contributing factor, spontaneous remission occurring more frequently in younger infected individuals. Chronic hepatitis C is often asymptomatic and can be mild; but in 20 percent of patients, the chronic infection leads to progressive liver disease and ultimately cirrhosis and end stage-liver disease. These conditions increase the risk of developing hepatocellular carcinoma (HCC) [8]. There is little evidence that the risk of progression of liver disease is affected significantly by virologic factors, including viral levels in the serum, viral genotype, and quasispecies diversity. However, many host factors have been found to increase this risk, including older age, male gender, and an immune suppressed state, such as HIV co-infection. Environmental factors also complicate the course of chronic hepatitis C like alcohol, iron overload, obesity, nonalcoholic fatty liver disease, schistosomal co-infection, hepatotoxic medications etc.

Although significant advances have been made in the development of treatments for chronic hepatitis C, their efficacy is not universal, and outcome of treatment is considerably affected by viral and host factors. In optimally selected patients, the best current therapies are effective in 40 to 50 percent of cases infected with viral genotype 1 and in 70 to 80 percent of those infected with genotype 2 and 3.

Current therapies for hepatitis C

The main goal for most patients is to eliminate HCV, completely and permanently. This is called a sustained virologic response (SVR). This is defined as a negative or undetectable HCV RNA test result six months after the end of treatment. A SVR means the body has cleared the virus, the person will always be antibody positive but will not have any active virus in his or her body. The goal of treatment is to eradicate HCV and prevent progression of liver disease. Other goals of therapy are to:

- minimize liver damage and prevent progression to end-stage liver disease
- improve the person's quality of life
- prevent the spread of HCV to other people by reducing the pool of infection

The two drugs currently available are IFN-α, a cytokine with immunomodulatory and antiviral activity, and ribavirin, a synthetic guanosine nucleoside analogue with in vitro antiviral activity [9]. After a 48-week course of parenteral IFN-α monotherapy, less than 20% of patients with persistent HCV infection clear the virus and show a sustained normalization of serum transaminase levels[10, 11]. A study on four-year follow up of treatment responders

suggests that patients with persistently undetectable HCV RNA are cured[12]. Ribavirin monotherapy has been shown to transiently decrease serum transaminase concentrations, but has no effect on serum viral load[13]. Combination therapy with IFN-α and ribavirin, however, increases sustained virological and biochemical response rates to between 40% and 50%[14, 15]. Patients with higher serum HCV RNA levels, severe hepatic fibrosis and significant siderosis, and men, are less likely to respond to treatment [11, 16].

Diagnosis

Laboratory testing

Two classes of assays are used in the diagnosis and management of HCV infection: serologic assays that detect specific antibody to hepatitis C virus (anti-HCV) and molecular assays that detect viral nucleic acid. These assays have no role in the assessment of disease severity or prognosis.

Serologic assays

Tests that detect anti-HCV are used both to screen for and to diagnose HCV infection. Anti-HCV can be detected in the serum or plasma using a number of immunoassays. Two enzyme immunoassays (EIAs) are approved by the U.S. Food and Drug Administration (FDA) for clinical use, Abbott HCV EIA 2.0 (Abbott Laboratories, Abbott Park, IL) and ORTHO_HCV Version 3.0 ELISA (Ortho-Clinical Diagnostics, Raritan, NJ), as well as one enhanced chemiluminescence immunoassay (CIA) VITROS_ Anti-HCV assay, (Ortho-Clinical Diagnostics, Raritan, NJ). The specificity of current EIAs for anti-HCV is greater than 99%[17].

Molecular assay

Qualitative assays have been more sensitive than quantitative assays. With the recent availability of real time polymerase chain reaction (PCR)-based assays and transcription-mediated amplification (TMA) assays, with sensitivities of 10-50 IU/mL, the need for qualitative assays has been decreased [18,19]. All currently available assays have excellent specificity, in the range of 98% to 99%. In 1997, the World Health Organization established the first International standard forHCVRNA nucleic acid technology [19] and the IU rather than viral copies is now the preferred unit to report test results [20,21]. For monitoring purposes, it is important to use the same laboratory test before and during therapy.

Genotyping assays

Genotyping is very useful in epidemiological studies as well as in clinical management for predicting the likelihood of response and determining the optimal duration of therapy. The hepatitis C virus can be classified into at least 6 major genotypes (genotypes 1 to 6) based on a sequence divergence of 30% among isolates [22]. Several commercial assays are available to determine HCV genotypes.

Diagnosis of acute and chronic HCV infection and interpretation of assays

The differentiation of acute from a chronic HCV infection depends on the clinical presentation, namely the presence of symptoms or jaundice, and whether or not there was a prior history of ALT elevation and its duration. After acute exposure, HCV RNA is usually detected in serum before antibody; HCV RNA can be identified as early as 2 weeks following exposure whereas anti-HCV is generally not detectable before 8-12 weeks. These two markers of HCV infection may be present in varying permutations, requiring careful analysis for interpretation (Table 1).

Liver biopsy

The biopsy is assessed for grade and stage of the liver injury, but it also provides information on other histological features that might have a bearing on liver disease progression [23]. The grade defines the extent of necroinflammatory activity, while the stage establishes the extent of fibrosis or the presence of cirrhosis. The most common method being the French METAVIR, the Batts-Ludwig, the International Association for the Study of the Liver (IASL) and the Ishak Scoring systems [24-28].

Identification of cases for treatment

Everyone infected with Hep C should be considered for treatment. For those people with active virus, the decision to access treatment is complicated. Many elements affect the success of treatment, from factors related to Hep C to pre-existing medical conditions to personal dynamics. Some of these factors can change over time while others remain constant, but each has a unique impact on treatment.

Disease factors

These factors are characteristics that relate directly to HCV and affect treatment success:

HCV genotype

- Genotypes 2 and 3 have treatment success rates as high as 80%, while treatment success is about 50% for genotype 1. The duration of treatment for genotypes 2 and 3 is shorter than for genotype 1.

HCV viral load

- Lower viral load at the start of treatment has a better chances of success.

Cirrhosis

- The longer a person has hepatitis C, the more likely it is they will develop inflammation, scarring, fibrosis and eventually cirrhosis of the liver. Treatment success is higher for people who have not progressed to cirrhosis.

The following conditions are often aggravated by treatment, can reduce treatment effectiveness and may cause some people to discontinue treatment:

Heart disease

- Ribavirin often causes anemia (low red blood cell counts) which can make existing heart conditions worse. In rare cases, peg-interferon can cause heart problems.

Kidney disease

- Because ribavirin is cleared from the body by the kidneys, renal dysfunction can result in a build-up of toxic levels of ribavirin. In these situations, the dose of ribavirin would be adjusted. Monitoring kidney function during treatment is important.

Depression

- It is a serious potential side effect of hepatitis C treatment .People who suffer depression while taking treatment, people who have thoughts of suicide or self-harm or people with a family history of depression should be encouraged to access support and counselling. Antidepressant medications can also be prescribed before and during treatment.

Glucose abnormalities

- Recent research has shown that glucose abnormalities can reduce the effectiveness of hepatitis C treatment. These abnormalities take the form of higher-than-normal glucose levels in the blood, insulin resistance or diabetes and can be related to other factors like obesity, age and triglyceride levels. Where possible, interventions that can stabilize glucose abnormalities will increase treatment success.

Personal factors

- Personal factors can affect treatment effectiveness, and attention should be given to those that can change over time:

Alcohol use

- Alcohol has serious impacts on treatment, so cutting back or stopping alcohol use is the best decision a person can make to contribute to treatment success.

Drug use

- Drug use also has serious impacts on treatment.

Finances

- Financial position is also an important factor before starting treatment and this may help stabilize a person's situation and prepare him or her for successful treatment.

Support systems

- People taking hepatitis C treatment must manage side effects and maintain adherence to their medications on a daily basis. Having the support of family, friends and a healthcare team that provides holistic care can help people achieve their goal of completing treatment.

Obesity

- People with a high body mass index (BMI) have lower success rates with HCV treatment.

Age

- Older age at time of infection and older age at the start of treatment are linked to lower rates of treatment success. Older people with hepatitis C are also at higher risk of having cirrhosis due to longer duration of infection.

Ethnicity

- Some studies of treatment show that Black people have less success at treatment. Although it is still a research

topic.

Sex

- Females generally have better response rates to treatment than males.

Contraindications

The only hard and fast rules for delaying or avoiding treatment are:

Pregnancy

- Ribavirin, is teratogenic, which means it can cause birth defects in fetuses. Pregnant women cannot start treatment until after childbirth. Both men and women must use effective birth control while on treatment and for at least six months after treatment is finished.

Children are generally not treated until they are older.

Treatment regimen

The best treatment results have been obtained using a combination of two medicines: peg-interferon (pegylatedinterferon) and ribavirin.

Peg-interferon

- Interferon is a naturally occurring chemical in the body that helps fight Hep C infection and protects cells from HCV. Peg-interferon is an engineered form of basic interferon with a polyethylene glycol (PEG) molecule attached to it to keep the blood levels of the drug higher for longer periods of time. This increases its presence and activity in the body. It is injected under the skin once a week. The optimal dose of peginterferon alfa-2b, is 1.5 µg/kg/week dosed according to body weight

Ribavirin

- Ribavirin is an antiviral medication that is a weak HCV fighter on its own but when combined with peg-interferon it is quite effective at helping reduce or eliminate HCV from the body. It is taken orally twice a day in a pill form and the dose used depends on the patient's weight (usually between 800–1,200 mg/day). The best treatment results have been obtained using a combination of pegylated interferon and ribavirin.

Length of treatment

- Treatment duration is determined by the genotype of the hepatitis C virus. Treatment for genotype 1 lasts 48 weeks (one year). Currently, genotypes 4, 5 and 6 are treated the same way as genotype 1. About 45% of people with genotype 1 will clear the virus. People with genotypes 2 and 3 respond better to the medications and are treated for 24 weeks (six months). About 80% of people with genotype 2 or 3 will eradicate the virus.

Managing side effects

-As with all medications, peg-interferon and ribavirin can cause side effects. Most side effects are mild and become easier to tolerate as treatment progresses but, occasionally, side effects can be severe enough to make it necessary to stop treatment.

Minor side effects

Flu-like symptoms include fever, sweating, chills, muscle aches and pains.

Hair loss or thinning of hair is a temporary side-effect. It can be severe but only in about 5% of patients on treatment.

Loss of appetite or nausea can make a person skip meals because they feel queasy, have an upset stomach or are just not hungry. This will impair their nutrition intake, which is an important part of living with hepatitis C.

Dry or itchy skin can be caused by the medications and by changes in a person's environment. Skin irritation may also be a result of injecting the peg-interferon.
Headaches can be a side effect of hepatitis C treatment.

Major side effects

These side effects can lead to very severe medical complications and are potentially life-threatening.

Depression and emotional changes can manifest themselves as despair, anxiety, irritability or suicidal thoughts.

Anemia and other blood changes like leukopenia or neutropenia and thrombocytopenia are a result of the way Hep C meds affect bone marrow.

Heart problems, such as arrhythmias can be caused by peg-interferon; some side effects of ribavirin, like anemia, can make existing heart conditions worse.

Hepatitis C meds can also cause auto-immune disorders, like rheumatoid arthritis.

Monitoring treatment response

Treatment success is predictable as early as four to 12 weeks into treatment. HCV RNA is usually done at four weeks and at 12 weeks. If the virus is undetectable at four weeks it is called rapid virological response (RVR). If at least 99% of the virus is cleared from the body at 12 weeks, it is called early virological response (EVR). Obtaining RVR or EVR is highly predictive of successful treatment. If a person does not get EVR at 12 weeks, it is likely their treatment will be stopped, as this person is not responding to treatment and will not achieve a sustained virological response. If a person does achieve EVR, the full course of treatment (as per genotype) will be completed to ensure that the virus is eradicated from the body. Laboratory monitoring should include measurement of the complete blood count, serum creatinine and ALT levels, and HCV RNA by a sensitive assay at weeks 4, 12, 24, 4 to 12 week intervals thereafter, the end of treatment, and 24 weeks after stopping treatment. Patients who achieve an SVR usually have improvement in liver histology and clinical outcomes [29, 30] (Table 3).

After treatment

Unsuccessful treatment

Non-Responders

Approximately thirty percent of patients treated with pegylated interferon and ribavirin are unable to clear virus from the serum [31,32]. For non-responders to standard interferon either with or without ribavirin, retreatment with peginterferon alfa-2a or 2b has been evaluated in three trials [33-35]. The SVR rates were higher among patients who had previously received interferon monotherapy, ranging from 20% to 40%, and were lower among non-responders to the combination of interferon and ribavirin, ranging from 8% to 10%. Persons more likely to achieve an SVR from retreatment included those with genotype non-1 infection, who had lower baseline HCV RNA levels, who had lesser fibrosis, who were of the Caucasian race, and whose prior treatment had consisted of interferon monotherapy [34].

Relapsers

- Virological relapse occurs within the first 12 weeks and late relapse,beyond 24 weeks, is extremely uncommon. Patients with virological relapse are likely to respond to the same regimen given a second time but will still experience an unacceptable rate of relapse. For relapsers to standard interferon and ribavirin, two regimens have been evaluated high dose peginterferon alfa-2b, 1.5 µg/kg/week with fixed dose ribavirin 800 mg daily, and low dose peginterferon alfa-2b, 1 µg/kg/week plus weight-based ribavirin, 1,000 to 1,200 mg daily [35].

Liver transplantation is an option for people with advanced liver disease and whose liver has ceased to function.

New therapies

Recent advances in the understanding of the HCV genome organization and life cycle and the development of HCV replicons and infectious viral particles in tissue culture systems [36-38] have enabled the rational design of agents that specifically inhibit HCV replication [39-41].

NS3/4A serine protease inhibitors (PIS)

Two major classes of PI molecules against HCV have been developed (Table 4). The first group is represented by noncovalent product-based inhibitors, such as ciluprevir and ITMN-191/R-7227. The second group is comprised of covalent reversible inhibitors, also known as serine-trap inhibitors. The most promising drugs in the latest class are telaprevir (TVR) and boceprevir [42].

NS5B RNA-dependent RNA polymerase inhibitors

HCV RNA-dependent RNA polymerase NS5B is the key viral enzyme responsible for HCV replication. It has been extensively characterized at a biochemical and structural level [42, 43, 44]. Two types of HCV polymerase inhibitors (nucleoside analogues and nonnucleoside analogues) are in development (Table 4).

Future directions

Drug resistant HCV is considered to be a major threat. Furthermore, many of the resistance mutations to PIs and nucleoside analogues may produce cross-resistance to other compounds within the same drug family,

which may complicate rescue-treatment options. The length of persistence of HCV resistance mutations after discontinuation of treatment are needed to be investigated. Most of the trials have tested new HCV inhibitors on HCV genotype 1; the efficacy of these drugs against other HCV genotypes is needed to be studied. Finally, the role of new STAT-C molecules in the treatment of nonresponders to IFN-based regimens or patients who experienced relapse has to be defined [45].

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Table 1. Interpretation of HCV assays

Anti-HCV	HCV RNA	Interpretation
Positive	Positive	Acute or chronic HCV depending on the clinical context
Positive	Negative	Resolution of HCV; Acute HCV during period of low-level viremia.
Negative	Positive	Early acute HCV infection; chronic HCV in setting of immunosuppressed state; false positive HCV RNA test
Negative	Negative	Absence of HCV infection

Adapted from Ghany et al. Hepatology, Vol. 49, No. 4, 2009

Table 2. Persons for whom HCV testing is recommended

• Persons who have injected illicit drugs in the recent and remote past, including those who injected only once and do not consider themselves to be drug users.
• Persons with conditions associated with a high prevalence of HCV infection including: o Persons with HIV infection o Persons with hemophilia who received clotting factor concentrates prior to 1987 o Persons who have ever been on hemodialysis o Persons with unexplained abnormal aminotransferase levels
• Prior recipients of transfusions or organ transplants prior to July 1992 including: o Persons who were notified that they had received blood from a donor who later tested positive for HCV infection o Persons who received a transfusion of blood or blood products o Persons who received an organ transplant
• Children born to HCV-infected mothers
• Health care, emergency medical and public safety workers after a needle stick injury or mucosal exposure to HCV-positive blood
• Current sexual partners of HCV-infected persons

Table adapted from "Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease." Centers for Disease Control and Prevention. MMWR Recomm Rep 1998;47(RR-19):1-39.

Table 3. Virological responses during therapy and definitions

Virological Response	Definition	Clinical Utility
Rapid virological response (RVR)	HCV RNA negative at treatment week 4 by a sensitive PCR based quantitative assay	May allow shortening of course for genotypes 2&3 and possibly genotype 1 with low viral load
Early virological response (EVR)	> 2 log reduction in HCV RNA level compared to baseline HCV RNA level (partial EVR) or HCV RNA negative at treatment week 12 (complete EVR)	Predicts lack of SVR
End-of-treatment response (ETR)	HCV RNA negative by a sensitive test at the end of 24 or 48 weeks of treatment	
Sustained virological response (SVR)	HCV RNA negative 24 weeks after cessation of treatment	Best predictor of a long-term response to treatment
Breakthrough	Reappearance of HCV RNA in serum while still on therapy	
Relapse	Reappearance of HCV RNA in serum after therapy is discontinued	
Nonresponder	Failure to clear HCV RNA from serum after 24 weeks of therapy	
Null responder	Failure to decrease HCV RNA by _ 2 logs after 24 week of therapy	
Partial responder	Two log decrease in HCV RNA but still HCV RNA positive at week 24	

Adapted from Ghany et al. Hepatology, Vol. 49, No. 4, 2009

Table 4. New specifically targeted hepatitis C virus drugs.

Protease inhibitors	Polymerase inhibitors	
Ciluprevira	Nucleoside analogues	Nonnucleoside analogues
ITMN-191/R-7227	Valopicitabinea	HCV-796a
Telaprevirb	R-1626/R-1479b	A-837093
Boceprevirb	R-7128/PSI-6130	XTL-2125a
GS-9132/ACH-806a	MK-0608	ANA-598
BI-1335		GS-9190a
TMC-435350		PF-00868554
MK-7009		VHC-759
		BI-1941
		MK-3281

Adapted from Soriano et al. CID 2009:48

a. Clinical development has been halted.
b. Compound in a more-advanced stage of clinical development.