HEPATITIS C VIRUS INFECTION: DIAGNOSIS AND TREATMENT

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Abstract

Hepatitis C virus (HCV) infection is becoming an increasing challenge to health professionals. The discovery of HCV in 1989 was a major breakthrough and it continues to be a major disease burden, affecting more than 170 million people worldwide. Of those exposed to HCV, 80% become chronically infected, and at least 30% of carriers develop chronic liver disease, including cirrhosis and hepatocellular carcinoma. HCV infection also increases the number of complications in persons who are co-infected with HIV. As our understanding of the disease evolves, so must our diagnostic and management strategies. This paper aims to review our current understanding of investigations and treatment options.

Introduction

HCV is an important human pathogen with global health effects and infects upto 3% of the general population worldwide. HCV infections frequently persist and can lead to cirrhosis and hepatocellular carcinoma. HCV was the first virus discovered by molecular cloning and found to be an RNA virus that belongs to Flaviviridae family and genus Hepacivirus[1] The discovery and characterization of HCV lead to the understanding of its primary role in post-transfusion hepatitis and its tendency to induce persistent infection. Different HCV isolates around the world show substantial nucleotide sequence variability. Based on the identification of these genomic differences, HCV has been classified into multiple strains. At least 6 major genotypes and more than 70 subtypes have been identified[2]. This has considerable importance in determining the outcome of treatment, although probably does not affect the natural history of the disease[3]. Though sequelae of HCV infection are more common than hepatitis B virus infection, even then, in Bangladesh due to lack of diagnostic facilities and awareness among medical professionals, HCV has been given less importance than hepatitis B virus. Our current review will highlight some important aspects of diagnosis and treatment of HCV infection.

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Diagnosis

Diagnostic tests for HCV infection are divided into serological assays for antibodies and molecular tests for viral particles. Screening assays based on antibody detection have markedly reduced the risk of transfusion related infection, and once persons seroconvert, they usually remain positive for HCV antibodies. However, recent data indicate that the level of HCV antibodies decreases gradually over time in few patients in whom infection spontaneously resolves[4]. In the 15% of the infected individuals who clear the virus spontaneously, these antibody tests will remain positive and thus cannot be used for determining active infection. This also applies to treated patients who clear the virus but remain positive for HCV antibody indefinitely.

The primary serologic screening assay for HCV infection is the enzyme immunoassay, for which there have been three consecutive versions with a resultant progressive increase in sensitivity. The currently used second- and third-generation enzyme immunoassays contain core protein as well as nonstructural proteins 3 and 4 (the third generation assay also contains nonstructural protein 5) and can detect antibodies within 4 to 10 weeks after infection. In low risk populations, the test misses only 0.5 to 1 percent of cases[5]. It can be falsely positive, especially in persons without risk factors and without signs of liver disease, such as blood donors or health care workers, and therfore, other tests must be used to confirm infection in these persons. Furthermore, false negative tests can occur in persons with immune compromise, such as HIV infection[6], patients with renal failure and those with HCV associated essential mixed cryoglobulinaemia[7].

The recombinant immunoblot assay (RIBA) has been used to confirm positive enzyme immunoassays. It uses antigens similar to those for the enzyme immunoassay but for an immunoblot format, so that responses to individual proteins can be identified. A positive assay is defined by the detection of antibodies against two or more antigens and an indeterminate assay by the detection of antibodies against a single antigen. The use of a

recombinant immunoblot assay to confirm results is recommended only in low risk settings such as blood banks[8]. However, with the availability of improved enzyme immunoassays and better RNA- detection assays, confirmation by RIBA may become less necessary[9].

In the past few years new assays based on the molecular detection of HCV RNA have been introduced. These tests can be categorized as qualitative and quantitative. Since viral RNA is unstable, the appropriate processing of samples is critical to minimize the risk of false positive results; samples to be tested should be separated and frozen within three hours after phlebotomy[10]. Qualitative HCV RNA tests are based on the PCR technique and have a lower limit of detection of fewer than 100 copies of HCV RNA per milliliter[11]. These are the tests of choice for the confirmation of viraemia and the assessment of treatment response. A qualitative PCR assay should also be used in patients with negative results on enzyme immunoassay in whom acute infection is suspected, in patients who have hepatitis with no identifiable cause, and in those with known reasons for false negative results on antibody testing.

The viral load has been shown to be relevant to the outcome of anti-HCV therapy[12,13] but not to predicting the likelihood of disease progression. Three commercial tests are currently available to quantitate the degree of viraemia: a branched-chain DNA assay and two assays involving reverse transcription PCR. Viral genotyping helps predict the outcome of therapy and influences the choice of the therapeutic regimen[12,13]. Different methods are available for the genotyping of HCV,[14] most of which are based on amplification by the PCR assay. These two (viral load and genotyping) are important predictors of the outcome of treatment, as response rates are directly linked to these variables. In addition, they influence the length of therapy: patients with genotype-1 and a high viral load are more resistant to therapy, with response rates in the order of 40% even after a year of combination treatment. By comparison, patients with genotype 2 or 3 may be expected to achieve sustained virologic response rates of nearly 80% after six months of treatment[15].

An important nonspecific laboratory test in HCV-infected persons is measurement of the alanine aminotransferase (ALT) level, an inexpensive and readily available means of identifying hepatic disease. It is the best test for monitoring HCV infection and the efficacy of therapy in the intervals between molecular testing. However in persons with HCV infection ALT levels may be normal or fluctuate, and therefore, a single normal value does not rule out active infection, progressive liver disease, or even cirrhosis. Similarly, the normalization of ALT levels with anti viral therapy is not proof of the success of therapy. Moreover, ALT levels may remain elevated for other reasons even after clearance of virus[16].

Histologic evaluation of a liver biopsy specimen remains the gold standard for determining the activity of HCV-related liver disease, and histologic staging remains the only reliable predictor of prognosis and the likelihood of disease progression[17]. A biopsy may also help to rule out other concurrent causes of liver disease. Therefore, biopsy is generally recommended for the initial assessment of persons with chronic HCV infection[8,16]. However, a liver biopsy is not considered mandatory before the initiation of treatment. It is useful in documenting the amount of ongoing destruction (grade) and degree of fibrosis (stage) of disease. Patients with more advanced fibrosis are at high risk of progressive liver disease, and therefore, should be considered strongly for therapy. Significant fibrosis may be present in patients with normal transaminase levels in up to 25% of patients. Conversely, patients with minimal fibrosis may choose to forego immediate therapy, in light of the side effect profile of current treatment as well as likelihood of response[18].

Treatment

Although acute HCV infection is uncommonly diagnosed, in natural history studies it has been shown to progress to chronic liver disease in up to 85% of patients. However, evidence suggests that interferon-based therapy given early in the course decreases the risk of progression to chronic infection.[19] Another unanswered question is whether post-exposure prophylaxis- for example, after a needle stick injury- is beneficial, as in the case of HIV infection. Currently no prophylactic regimen has been shown to be effective and efficient and only monitoring is recommended. So, health care workers, accidentally exposed to HCV infected blood via a needle stick injury, should be followed carefully for evidence of infection and treated then, rather than be given routine post-exposure prophylaxis.

The more common situation facing clinicians is that

of patients with chronic hepatitis C, for whom the goal of treatment is elimination of the virus. This is associated with stabilization or even improvement in liver histology and clinical course. Secondary aims are symptom control, improvement of liver function, and prevention of complications of progressive liver disease, and hepatocellular carcinoma. Most interventions apart from interferon-based therapy only marginal benefit.

Complete abstinence from alcohol is an extremely important behavioral modification, and has been shown to affect the likelihood of progression as well as impact the efficacy of therapy[20]. The utility of other therapies- including dietary supplements, herbs, and unconventional treatments- have not been rigorously studied, and the results are extremely varied[21]. Regardless of whether a patient elects to be treated or not, practice guidelines recommend that all patients with hepatitis C and no evidence for immunity be vaccinated for hepatitis A, and, if risk factors exist, for hepatitis B as well[22].

Treatment outcomes for patients treated with interferon are classified into nonresponse, relapse, and sustained virological response. A sustained virological response (SVR) is defined as undetectable virus in the serum 6 months after treatment completion, which correlates well with long-term absence of virus. Although any patient with hepatitis C infection can be considered for therapy, the decision must be individualized, based on the overall risks and benefits of therapy. Patients with detectable HCV RNA, elevated serum aminotransferase levels, evidence of chronic hepatitis on liver biopsy, absence of decompensation, and no contraindication (Table-1), should be offered combination alpha interferon and ribavirin therapy.

Factors predicting a therapeutic response include low pretreatment HCV RNA level, genotypes 2 or 3, female gender, low body mass index (BMI) and low hepatic iron load. Patients with advanced liver disease or decompensated cirrhosis are also unlikely to respond, and frequently are unable to tolerate treatment[15]. Treatment of hepatitis C infection has evolved over the last 15 years. It remains based on interferon alfa, as an immune modulator. Response rates were modest when it was used as monotherapy (10% in genotype 1 and at best 30% in genotype 2 and 3). Side effects remain a significant problem (Table-II).

The addition of ribavirin, a nucleoside analogue and an inhibitor of viral replication improved the SVR rate to around 40% (20% in genotype 1 and 65% in genotype 2 and 3). There is some evidence for a dose-response effect, with generally increased response rates in higher doses (typically 1000 to 1200 mg in divided doses)[23].

Treatment consists of 3 million U of interferon alfa administered subcutaneously three times a week and 1200 mg of ribavirin orally per day for patients who weight at least 75 kg and 1000 mg of ribavirin orally per day for those weighting less than 75 kg. Usually ribavirin is taken in divided doses, given in the morning and evening, and interferon is given before bedtime.

The most recent innovation in treatment was the introduction of pegylated interferon, a form of interferon covalently bound to a large, inert polyethylene glycol molecule. The combination serves to reduce clearance rates, and thereby increase the duration of action. Enhanced response

Table- I: Contraindications to treatment with Interferon Alfa and Ribavirin

Contraindication	Interferon Alfa	Ribavirin
Absolute	Current psychosis or a history of psychosis	Pregnancy
	Severe depression	Absence of use of a reliable
	Neutropenia or thrombocytopenia	form of contraception
	Symptomatic heart disease	End stage renal failure
	Decompensated cirrhosis	Anaemia
	Uncontrolled seizures	Haemoglobinopathies
	Organ transplantation (other than liver)	Severe heart disease
Relative	Autoimmune disorders (eg, thyroiditis)	Uncontrolled hypertension
	Uncontrolled diabetes	Old age

Table –II: Side effects of treatment with interferon Alfa and Ribavirin

Frequency of side effects	Interferon Alfa	Ribavirin
>30% (Very Common)	Influenza-like symptoms Headache Fatigue Fever Rigors Myalgia Thrombocytopenia Induction of autoantibodies	Haemolysis Nausea
1-30% (Common)	Anorexia Erythema at injection site Insomnia Alopecia Lack of motivation Inability to concentrate Irritability Emotional liability Depression Diarrhoea Induction of autoimmune disease Leukocytopenia Taste perversion	Anaemia Nasal congestion Pruritus
<1% (Rare)	Polyneuropathy Paranoia or suicidal ideation Diabetes mellitus Retinopathy Optic neuritis Hearing impairment Seizures Loss of libido Cardiotoxicity	Gout

Table-III: Sustained Viral Response rate of HCV with different therapeutic regimens[24, 25]

Therapeutic regimen	# of months	% SVR Genotype 1	% SVR Genotype 2 or 3
Interferon	6	10	20
INF/Riba	6 to 12*	29	66
Peg INF	6 to 12*	20	40
Peg INF/Riba	6 to 12*	50	88

*HCV genotype 1 treated for 12 months and genotype 2 or 3 for 6 months

rates have been demonstrated for both commercially available pegylated interferons with the best response rate evident in combination therapy with ribavirin[26, 27]. If patients are able to complete a full course of treatment at optimal doses (eg, not require dose adjustments for side effects or toxicity), sustained virological response rates may range as high as 88% in genotype 2 and upto 50% of those with genotype 1 (Table-III). Side effects such as injection site reaction and bone marrow suppression may be more pronounced with different formulations and doses.

Although the usual duration of treatment for patient

with genotype 1 is 48 weeks, data from multiple studies suggest that it is possible to predict the outcome of therapy by 12 weeks of therapy. If a patient fails to either clear infection or have at least a two log decline in the viral load (measured with the same assay as used at baseline), it is unlikely that the patient will develop a sustained virological response[24]. The virological response to combination therapy should be assessed at week 24, since elimination of the virus can occur late with this approach. Persons with a positive PCR assay for HCV RNA at week 24 should be considered to have had no response to treatment, and therapy should be discontinued. Those infected with HCV genotype 2 or 3 who have a negative PCR assay for HCV RNA can also usually stop therapy at this time, but an additional 24 weeks of treatment is suggested for patients with other genotypes and a negative PCR assay[28, 29].

Patients on therapy need to be monitored closely for complications or symptoms of the adverse reactions of combination therapy. This should include evaluation for depression, symptoms of irritability, sleep disturbance, visual disturbances, as well as evidence of hyper or hypothyroidism, etc. Blood counts should be monitored frequently at the beginning of treatment and at least monthly afterwards, if patient is stable.

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