

# HEPATITIS C

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## INTRODUCTION

Hepatitis C virus (HCV) is a single stranded virus of flaviviridae family.<sup>1</sup> It was identified in 1989 as the casual agent of most cases of post-transfusional and sporadic acute and chronic viral hepatitis.<sup>2</sup> A wide variety of hepatitis C virus types resulted from frequent mutation in the genome of the virus. These variations are classified as HCV genotypes designated 1-6.<sup>3</sup> In United States 75% of patients are genotype 1a and 1b,<sup>4</sup> while genotype 3 is the most prevalent HCV type in Pakistan.<sup>5</sup> HCV is widely prevalent throughout the world and it is estimated that 3% of the population, about 170 million people, have chronic HCV worldwide.<sup>6</sup>

The prevalence of HCV is 0.5 to 8% in blood donors in different parts of the world.<sup>7</sup> Studies from Pakistan on blood donors show 9% anti-HCV positivity in professional blood donors while 4% and 8% for healthy family and volunteer blood donors respectively.<sup>8</sup> Reports from other studies indicate 51% seropositivity of hepatitis C in chronic liver disease, 57% in cirrhosis and 14% in hepatocellular carcinoma.<sup>9</sup> According to recent data anti-HCV prevalence in obstetric cases is 6.6%<sup>10</sup> and 5.31%<sup>11</sup> in the general population. The current prevalence in Pakistan varies from 3 to 7% in different parts of the country.<sup>12</sup> The spread of HCV is primarily parenteral. Patients at the highest risk for acquiring hepatitis C are intravenous drug users (90%), persons requiring multiple transfusions of blood or blood products such as haemophiliacs and patients undergoing major surgery. Household contacts appear to be at low risk and transmission by sexual or intimate contact (0.4 to 3%) occurs much less frequently than HBV.<sup>13</sup> Perinatal transmission occurs in approximately 3 to 5% of infants born to mothers infected with HCV.<sup>14</sup> The risk of transmission of HCV from needle stick injury is 5%.<sup>15</sup> Although HCV has been found in saliva and milk but transmission via breast milk has not been documented and it is not contraindicated.<sup>16</sup> The incubation period between exposure to HCV and the appearance of clinical evidence of acute viral hepatitis averages 6 to 7 weeks.<sup>17</sup> The first serological marker of infection is HCV RNA. This is followed by the appearance of anti-HCV, which is detectable within 2 to 3 months after HCV RNA. However these antibodies are neither neutralizing

nor protective and 85% of HCV infection assumes a chronic phase.<sup>6</sup>

## CLINICAL FEATURES

Most patients (84%) infected with HCV never develop a clinical syndrome of acute hepatitis. Diagnosis requires PCR for HCV RNA since acute infections may be seronegative for anti-HCV. Irrespective of the patients age at acquisition and the mode of viral transmission 85% of HCV infections enter a chronic phase and 15% will spontaneously clear the virus.<sup>18</sup> Many patients remain asymptomatic for years and are only detected on health screening or at the time of blood donation.

The most common symptoms of the chronic HCV are nonspecific malaise, fatigue, insomnia and right upper quadrant abdominal pain. Some patients may remain asymptomatic even if the disease progresses to cirrhosis.<sup>6</sup> Approximately 20 to 50% of chronic HCV patients develop cirrhosis over 10 to 20 years of infection.<sup>18</sup> Extra hepatic manifestations develop in approximately 15% of patients and these include cryoglobulinaemia, membranous glomerulonephritis, thyroiditis, porphyria cutanea tarda, idiopathic pulmonary fibrosis and monoclonal gamopathies.<sup>19</sup> Hepatic steatosis is a particular feature of infection with HCV genotype 3.<sup>20</sup> HCV increases the risk of hepatocellular carcinoma (HCC). It is estimated that between 2 to 6.7% of all the patients with HCV cirrhosis will develop HCC over 10 years and the annual risk is 1 to 4%. Both HCV and HBV infections are the leading causes of HCC in Pakistan. HCV accounted for 41% of HCC and coinfection with HCV and HBV accounted for 7% of HCC.<sup>21</sup>

**Investigations:** The first step in diagnosis of HCV infection is the detection of Anti-HCV by ELISA which is >99% sensitive and specific.<sup>22</sup> The second main step in diagnosis of chronic HCV infection is the detection of HCV RNA by PCR. Virus is generally detectable 7 to 21 days following exposure. Liver biopsy plays an essential role in the diagnosis and management of chronic HCV. The severity of histologic injury correlates poorly with symptoms. But because of high response rates to treatment in patients infected with HCV genotypes 2 or 3, treatment may be initiated in these patients without liver biopsy.

**Treatment:** The aims of treatment are:

1. Viral eradication.
2. Prevention or regression of fibrosis.
3. Prevention of HCC.

Patients less than 40 years of age show better response as compared with elderly. Young females tend to do well with treatment. High level of viraemia is associated with poor response. Genotypes 2 and 3, which are prevalent in Pakistan, show good response to treatment.<sup>23</sup> Genotypes 1, especially 1b show worst outcome.

Immunodeficiency, excess of alcohol consumption and coinfection with HIV or HBV, all adversely effect the outcome to HCV infection.<sup>24</sup>

Interferon (INF) alpha is the backbone of treatment for chronic HCV. It is a glycoprotein. It is anti viral and also enhances immune response to viruses. However interferon 2b monotherapy 3 MIU thrice a week for 12 months give 12% sustained virological response (SVR).<sup>25</sup>

Later on therapy with interferon in combination with ribavirin becomes the gold standard. Interferon 3 MIU thrice weekly along with ribavirin 800 to 1200 mg daily. The sustained virological response improves to 38 to 43%. SVR also depends on genotype of the virus. Genotype 1 required treatment of the patients for 48 weeks to achieve SVR of 29% and Genotype 2 and 3 the SVR of 66% after 24 weeks of treatment.<sup>26</sup>

A combination of pegylated interferon and ribavirin is now the standard therapy. This combination achieves SVR of 80% for genotypes 2 & 3 and 50% for genotype 1. Pegylated have a covalently attached polyethylene glycol.<sup>6</sup> It was approved by FDA in 2001. Two types of pegylated INF are currently available:

1. Peg INF Alfa 2a (40 KD)
2. Peg INF Alfa 2b (12 KD)

Both Peg INF-2a and Peg INF-2b have a decreased systemic clearance rate and a prolonged plasma half-life (approx. 10 fold) compared with standard INF. This allows once weekly dosing with the pegylated formulation.

Peg INF alfa 2a is predominantly metabolized in the liver, whereas the kidneys eliminate Peg INF alfa 2b predominantly. Initial clinical trials demonstrated that monotherapy with Peg INF 2a or Peg INF 2b improved SVR rates compared with standard INF.<sup>27</sup>

Even in patients of liver cirrhosis, 30% of patients had a sustained virologic response when

treated with 180 mcg Peg INF alpha 2a once weekly for 48 weeks.<sup>28</sup> But this sustained virologic response rate could be increased to more than 50% by combination with ribavirin.<sup>27</sup>

Patients infected with 1a or 1b are treated for 48 weeks. While patients with cirrhosis or a high viral level in serum (>850000 IU/ml) may require 48 weeks of treatment. Those infected with genotype 2 or 3 without cirrhosis or with low levels of viraemia are treated for 24 weeks and require a ribavirin dose of only 800mg.<sup>27</sup>

#### **New modalities of treatment:**

Ribozyme targets HCV RNA by cleaving specific RNA sequences.<sup>29</sup>

Levovirin may be used instead of ribavirin as it causes less haemolysis.

Thymosine alpha is an immune modulator, which is showing promise.

Antifibrotic agent colchicine is on trial.

Interleukin-10 may normalize ALT, improve liver histology and even reduce fibrosis.

#### **CONCLUSIONS**

1. Education and counseling of patients are the major aspects of HCV treatment.
2. Patients with HCV should be vaccinated against hepatitis A and B.
3. Avoidance of alcohol is recommended.
4. Screening for HCC, in cirrhosis patients is recommended with Alfa-foetoprotein (AFP) and abdominal U/S every six months.
5. Blood donor screening can reduce HCV incidence.
6. Currently there is no vaccine available.
7. As in Pakistan genotypes 2 & 3 are common and standard interferon in combination with ribavirin has a response rate >66%, which is almost close to pegylated interferon, so patients should be treated with conventional interferon because it is less costly as compared to peg interferon.
8. Levovirin can be used instead of ribavirin as it causes less haemolysis.

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