CHAPTER (1)

INTRODUCTION

The existence of hepatitis C virus (HCV), originally "non-A non-B hepatitis" was postulated in the 1970s and proved in 1989 ***(Houghton, 2009).*** It is a small enveloped single stranded RNA virus of the family Flaviviridae and genus Hepacivirus ***(Indolfi and Resti, 2009).***

HCV is a major cause of liver disease worldwide and a potential cause of substantial morbidity and mortality ***(Shepard et al., 2005).***

HCV viral kinetics have been analysed in a large number of studies for prediction of treatment response and non response with the aim to establish algorithms for individualized treatment durations ***(Zeuzem et al., 2001 and Jessner et al., 2003).***

Mathematical models of HCV kinetics provide a means of estimating the antiviral effectiveness of therapy, the rate of virion clearance and the rate of loss of HCV-infected cells. They have also proved useful in evaluating the extrahepatic contribution to HCV plasma viremia and they have suggested mechanisms of action for both interferon (IFN) and ribavirin (RBV) in the treatment of chronic HCV infection ***(Dahari et al., 2008).***

Epidemiology of HCV

An estimated 180 million people worldwide are infected with hepatitis C. Hepatitis C is not known to cause disease in other animals. No vaccine against hepatitis C is available ***(Houghton, 2009).***

It is difficult to determine the number of new HCV infections, as most acute cases will not be noticed clinically. Fewer than 25% of acute cases of hepatitis C are clinically apparent. In addition, the age of infection upon diagnosis is not possible to determine in most cases. Nevertheless, it has to be assumed that the number of new infections has considerably decreased over the past decades ***(Wasley et al., 2008).***

It is estimated that only one out of four individuals infected with HCV is aware of the disease and so most of the infected patients can not take advantage of treatment options and risks of further transmission of the virus do exist ***(McHutchison, 2004).***

The epidemiology of HCV in Egypt

Egypt has the highest prevalence of antibodies to HCV in the world, estimated nationally at 14.7% and an estimated 9.8% are chronically infected ***(Miller and Abu-Raddad, 2010).***

An epidemiological study has suggested that more than half a million people get infected annually with HCV in Egypt. Around 75% of all cases of liver cirrhosis and liver cancer in Egypt and the Middle East are caused by hepatitis infections ***(El-Zanaty et al., 2009 and Kohaar et al., 2010).***

Antischistosomal therapy has been the main cause of contamination in Egypt. In fact, epidemiological and molecular evolutionary studies in Egypt relate the origin of the HCV genotype 4 (HCV-4) epidemic to the mass campaigns of intravenous treatment of Schistosomiasis in rural areas in the 1960s to 70s ***(Frank et al., 2000).***

Evidence suggests that HCV transmission occurred due to insufficient sterilization of injection equipments between patients.

This mode of HCV transmission was cut after 1982 when oral praziquantel was introduced for Schistosomiasis treatment ***(El Katsha et al., 2006).***

Procedures performed by non-medical professionals and traditional healers such as dental care, wound treatment, circumcision, deliveries, excision and scarification have all been identified as important risk factors for HCV transmission in Egypt ***(Stoszek et al., 2006).***

The institution of volunteer blood donation, creation of recombinant clotting factors, and implementation of HCV blood testing (between 1990 and 1992) dramatically decreased transfusion-acquired HCV infection **(*Esteban et al., 2008*).**

Viral structure

HCV is a small-enveloped virus with one single-stranded positive-sense RNA molecule of approximately 9.6 kb. It is a member of the Flaviviridae family. This viral family contains three genera, flavivirus, pestivirus, and hepacivirus ***(Thiel et al., 2005).***

The HCV particle consists of a core of genetic material (RNA), surrounded by an icosahedral protective shell of protein, and further encased in a lipid (fatty) envelope of cellular origin. Two viral envelope glycoprotein, E1 and E2, are embedded in the lipid envelope ***(Op De Beeck and Dubuisson 2003).*** E1 and E2 are transmembrane glycoproteins essential for viral attachment, entry and fusion ***(Lindenbach et al., 2005).*** **Figure (1)**

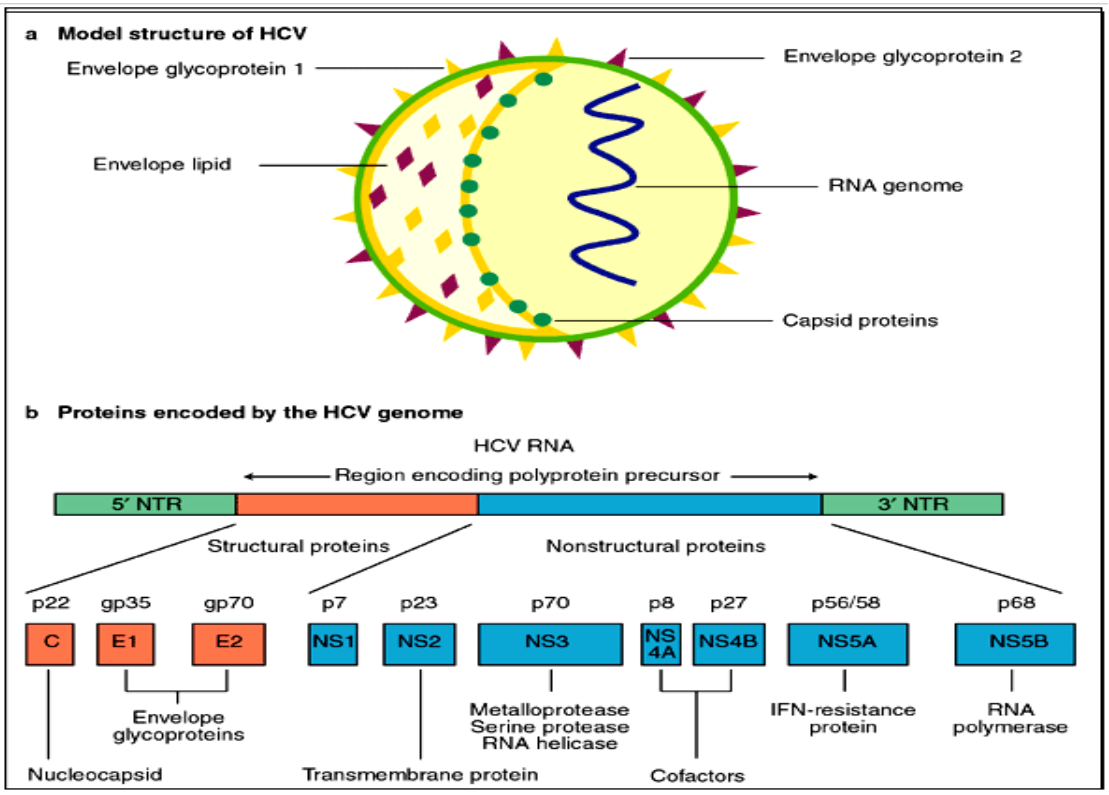

Fig.(1): Model structure and genome organization of HCV.
(http://www.expertreviews.org/ Molecular medicine).

Genotypes and quasi-species

Comparisons of HCV nucleotide sequences derived from individuals from different geographical regions revealed the presence of six major HCV genotypes namely 1,2,3,4,5,6 with a large number of subtypes within each genotype ***(Simmonds et al., 2005).***

The distribution of genotypes varies by geographical location and risk groups for infection. HCV-4, for example, is found mainly in Egypt, the Middle East, and Central Africa ***(Wasley and Alter, 2000).***

Genotype 6 (HCV-6) is found predominantly in Asia. The distribution of genotypes is ever changing with immigration and

alterations in the primary modes of viral transmission. Therefore, the frequencies of viral genotypes change over time ***(Esteban et al., 2008).***

Modes of transmission

HCV is predominantly transmitted by the parenteral route in procedures such as unscreened blood transfusions, injections related to intravenous drug use (IDU), injections related to health-care procedures, invasive medical and surgical interventions and to a lesser extent, other percutaneous exposures ***(Rantala and Van de Laar, 2008).***

Clinical presentation

HCV is often diagnosed accidentally and, unfortunately, remains heavily under-diagnosed ***(McHutchison, 2004).***

The spectrum of clinical manifestations of HCV infection varies in acute versus chronic disease. In acute infection, the majority of newly-infected patients will be asymptomatic and have a clinically non apparent or mild course. Jaundice as a clinical feature of acute HCV infection, will be present in less than 25% of infected patients. Other symptoms that may occur and are similar to those in other forms of acute viral hepatitis, including malaise, nausea, and right upper quadrant pain ***(Chu, 1999).***

The risk of chronic HCV infection is high. About 80-100% of patients remain HCV RNA positive after acute HCV infection ***(Alter, 1999).*** Most of these will have persistently elevated liver enzymes in further follow-up. Most patients with chronic infection

are asymptomatic or have only mild nonspecific symptoms as long as cirrhosis is not present The most frequent complaint is fatigue. Less common manifestations are nausea, weakness, myalgia, arthralgia, and weight loss ***(Lauer and Walker, 2001).***

The risk of developing cirrhosis due to chronic HCV infection ranges from 5% to 25% over periods of 25 to 30 years ***(Liang et al., 2000).***

Possible signs and symptoms of liver cirrhosis include ascites, bruising and bleeding tendency, jaundice, portal hypertension, varices and hepatic encephalopathy ***(Munteanu et al., 2006).***

Several extrahepatic manifestations, such as cryoglobulinemia, non-Hodgkin's lymphoma, membranoproliferative glomerulonephritis or porphyria cutanea tarda, have been reported in the natural history of HCV infection ***(Pischke et al., 2008).***

Diagnosis

Chronic hepatitis C should be considered in every patient presenting with clinical, morphological or biological signs of chronic liver disease. For the diagnosis of hepatitis C both serologic and nucleic acid-based molecular assays are available ***(Scott and Gretch, 2007).***

1- ***Serologic Assays***

That detect specific antibody to hepatitis C virus (anti-HCV). Serologic assays that detect anti-HCV are used both to screen for and to diagnose HCV infection ***(Colin et al., 2001).***

When anti-HCV antibodies are detected, the presence of HCV-RNA has to be determined in order to discriminate between chronic hepatitis C and resolved HCV infection ***(Everson et al., 2005).***

HCV core antigen (HCVcAg) test has been introduced to supplement anti-HCV test or HCV-PCR over the last decade, and could be used for the monitoring of antiviral therapy as well as for the diagnosis of HCV infection ***(Morota et al., 2009).***

2- The OraQuick HCV Rapid Antibody Test

Is used to test individuals who are at risk for infection with HCV and people with signs or symptoms of hepatitis. The test strip can be used with a sample collected from saliva, whole blood, serum, or plasma . OraQuick is a test strip and does not require an instrument for diagnosis. It takes about 20 minutes to obtain results from the test ***(Lee et al., 2011).***

3- *Molecular Biology Assays*

Are used to detect and quantify HCV-RNA and to determine HCV genotype. Target amplification methods e.g., polymerase chain reaction (PCR) or transcription mediated amplification (TMA) and signal amplification methods e.g., the branched DNA assay (bDNA) can be used to detect and quantify HCV-RNA ***(Pawlotsky, 2002).***

4- Liver biopsy

Liver biopsies show various histologic features that most often involve both the portal tracts and parenchyma. It also allows to determine the necro-inflammatory activity (grading) and the degree of fibrosis (staging) as well as to recognize or exclude coexisting

liver pathology, such as alcoholic liver disease, iron overload or non alcoholic fatty liver disease (NAFLD) ***(Pinzani et al., 2008 and Lefkowitch, 2010).***

Management of HCV Infection

Aim of treatment

Treatment of chronic HCV infection has 2 goals:

The first is to eradicate the virus, a consequence of achieving this goal is to prevent progression to cirrhosis, decompensated liver disease and hepatocellular carcinoma (HCC) ***(Ghany et al., 2009).***

The second goal is to achieve sustained eradication of HCV i.e sustained virologic response (SVR), which is defined as the persistent absence of HCV RNA in serum 6 months or more after completing antiviral treatment ***(Abdelmalek et al., 2004 and Desmond et al., 2006).***

Standard therapy of chronic hepatitis C

The current standard of care for the treatment of HCV infection is the combination of a pegylated interferon (PEG IFN) administered subcutaneously once per week and ribavirin taken orally every day. The dose of interferon is the same for all HCV genotypes ***(Hadziyannis et al., 2004).*** The currently used types of PEG IFN for treatment of HCV infection are PEG INF alfa-2a (administered at a fixed dose of 180 mcg once per week given subcutaneously) together with ribavirin 1000 to 1200 mg daily, 1000 mg for those who weigh < 75 kg and 1200 mg for those who weigh >75 kg ***(Fried et al., 2002),***

and PEG INF alfa-2b (administered at a dose of 1.5 mcg per kg subcutaneously once per week dosed according to body weight). Although the dose of ribavirin used in the original registration trial was fixed at 800 mg daily, a subsequent community-based study of patients with genotype 1 infection demonstrated that weight-based ribavirin (800 mg for patients <65 kg; 1000 mg for patients weighing 65 to 85 kg; 1200 mg for patients weighing 85 to 105 kg; and 1400 mg for patients weighing >105 kg but <125 kg) was more effective ***(Manns et al., 2001 and Jacobson et al., 2007).***

This combination has a number of side effects that are dominated by fatigue, influenza-like symptoms, haematologic abnormalities, endocrine and neuropsychiatric symptoms ***(Patel et al., 2006 and Jacobson et al., 2007).***

Treatment is administered for 48 weeks in patients with genotype 1 or 4 infection and 24 weeks in those with genotype 2 or 3 infection ***(Hadziyannis et al., 2004).***

Contraindications to the combined IFN-RBV therapy

Treatment is contraindicated in the presence of pregnancy, severe depression, significant neuropsychiatric syndromes, alcohol abuse, drug addiction, active autoimmune diseases such as lupus erythematosus, rheumatoid arthritis or psoariasis, severe anaemia, liver failure, failure to apply effective contraceptive measures during treatment and 6 months after, uncontrolled hypo or hyperthyroidism and recent organ transplantation ***(Bini et al., 2005 and Delwaide et al., 2005).***