INTRODUCTION

Hepatitis C virus (HCV) infection is a major health problem throughout the world. Recent estimates indicate that 175 million people are infected ***(Hnatyszyn, 2005).***

More than 90% of HCV isolates from Egyptian patients are of the genotype 4 variant, which is significant considering Egypt has the highest worldwide prevalence of HCV (10-20%) ***(Kamal and Nasser, 2008).*** In rural areas of Egypt, the prevalence of HCV reaches 24%. Other countries where genotype 4 is prevalent include the equatorial and west-central African nations of Gabon, Tanzania, Libya, and Zaire, where seroprevalence can go up to 8% ***(Abdel-Aziz et al., 2000).***

In Egypt, viral transmission occurs mainly via blood transfusion, through nosocomial exposure, and during circumcision with the use of nonsterilized equipment. Intrafamilial exposure is also a primary route of transmission in rural Egypt, and having an anti-HCV positive family member is among the strongest predictors of HCV in Egypt ***(Mohamed et al., 2005).*** Also, history of schistosomiasis and parenteral antischistosomal therapy is significantly associated with HCV in Egypt ***(Kamal et al., 2006).***

Antiviral therapy for chronic hepatitis C has many goals; the primary goal is durable viral clearance as evidenced by the absence of HCV RNA in serum (virological response); the secondary goal is reduction of damage to the liver as

determined by either persistently normal ALT levels (biochemical response) or improved liver biopsy, with the expectation that this will delay or prevent cirrhosis, HCC, the need for liver transplantation, and death, as well as to prevent the spread of the virus to other persons, improve the patient's quality of life and prevent progression to end stage liver disease ***(Manns et al., 2006).***

Early reports indicated that patients with genotype 4 HCV infection responded as poorly to interferon monotherapy as patients with genotype 1, with sustained virologic response rates (SVRs) of 5-10% ***(Kamal et al., 2000b).*** In comparative clinical studies, SVRs improved (range 8-42%) in patients with genotype 4 infection with the addition of ribavirin to interferon alfa ***(Koshy et al., 2002).***

Rapid and Early virologic response defined as undetectable HCV RNA at weeks 4 and 12 respectively have been shown as important tools for determination of duration of therapy. In chronic hepatitis C genotype 4 and undetectable HCV RNA at weeks 4 and 12, treatment with PEG-IFN alpha-2b and ribavirin for 24 weeks and 36 weeks, could be sufficient ***(Ferencie et al., 2008)***

Side effects of treatment are essentially universal. These led to modification of the dosage of interferon and/or ribavirin in 35-42% of patients treated with pegylated interferon in large, randomized clinical trials and discontinuation of therapy in 14-19% of these patients ***(Fried et al., 2002).***

The most common side effects reported in previous clinical trials are:

1- **Constitutional symptoms:** like ***fatigue***, ***headache***, ***myalgias*** which are mainly side effects of interferon-alpha, stimulation of immune response leads to release of cytokines and other factors that may cause fatigue and headache. Fatigue and headache are also related to the anemia caused by ribavirin.

Fever is principally a side effect of interferon, and tends to be worse in the first few injections ***(Hadziyannis et al., 2004).***

2- **Gastrointestinal symptoms:** like ***nausea***, ***anorexia*** and ***diarrhea***: were reported in about 20% of patients on therapy ***(Fried et al., 2002).***

3- Psychiatric side effects:

The most common is ***insomnia*** which may occur in 40% of patients. Insomnia can be contributed to fatigue, headache, irritability, depression, or other side effects. Another very common side effect is ***irritability*** documented in clinical trials in 30% of patients, but may be present to a lesser degree in most patients. ***Depression*** develops in 20-35% of patients treated with interferon and ribavirin. This can be one of the major morbidities associated with treatment. Practitioner screening for the development of suicidal or other destructive ideation is essential when patients develop symptoms of

depression. Co-management of patients with a prior history of depression or other mental illness by mental health professionals, with appropriate therapy before treatment is very important ***(Hauser, 2004).***

4- Dermatological side effects:

Approximately one third of patients develop ***noticeable hair loss*** while on therapy. 20-25% of patients develop ***a skin rash***. Which is generally due to ribavirin. It is a fine, red, petechial rash. Tends to be seen over the arms and trunk. Although it may be present diffusely, it tends to improve and recur spontaneously during treatment ***(Hadziyannis et al., 2004).***

5- Haematological side effects:

Anemia: Ribavirin causes a dosage-dependent hemolytic anemia. Interferon can suppress bone marrow production of red blood cells. This results in anemia, likely in >20% of patients treated with a pegylated interferon and ribavirin.

Neutropenia: Interferon suppresses bone marrow production of leukocytes which leads to neutropenia in approximately 20% of treated patients.

Thrombocytopenia: Platelet counts often drop in the setting of interferon and ribavirin therapy due to interferon suppression of platelet production in the bone marrow ***(Manns et al., 2001 and Torriani et al., 2004).***

6- Other side effects:

Dyspnea: While the incidence of dyspnea was not uniformly reported in clinical trials, this is a common side effect of therapy. It is often linked to the severity of anemia with its accompanying decreased oxygen-carrying capacity leading to dyspnea on exertion. Dyspnea may also occur due to interstitial pneumonitis ***(Torriani et al., 2004).***

Cardiac: arrhythmias, angina or even myocardial infarction may occur ***(Hadziyannis et al., 2004).***

Visual changes: are fairly common but the exact incidence is unknown. The most commonly documented eye complications are “cotton wool spots” and retinal hemorrhages but most interferon-related retinopathy is asymptomatic and reversible ***(Hayasaka et al., 1998).***

Thyroid Dysfunction: Interferon therapy can be associated with changes in thyroid function due to induction of autoimmune thyroid disease (usually hypothyroidism, but hyperthyroidism may occur). Such changes are more common in patients with a history of thyroid dysfunction ***(Andrade et al., 2008).***

AIM OF THE WORK

The aim of this work is to describe side effects which may occur due to Interferon/ Ribavirin therapy in Egyptian HCV patients.

Chapter one

VIROLOGY OF HEPATITIS

Structure of hepatitis C virus:

HCV is a positive strand RNA virus that has been classified as the genus Hepacivirus in the Flaviviridae family. The HCV genome is an uncapped, linear molecule with length of_9600 nucleotides it carries a long open reading frame that is flanked at the 5_- and 3_-ends by short highly structured non-translated regions (NTRs). The 5_-NTR has a length of about 340 nt and contains an internal ribosome entry site (IRES) required for translation of the HCV genome ***(Bartenschlager et al., 2004).*** This RNA element binds the 40 S ribosomal subunit in the absence of other translation initiation factors in a way that the initiation codon is placed in the immediate vicinity of the P site ***(Pisarev et al., 2005).***

Part of the IRES (domain II) overlaps with RNA signals essential for viral replication arguing for a possible role of domain II in regulating a translation-RNA replication switch.

The 3_-NTR has a tripartite structure composed of a _40-nt-long variable region downstream of the HCV coding sequence, a poly (U/UC) tract of heterogeneous structures of CREs length, and a highly conserved 98-nt-long sequence designated X-tail (Fig. 1). Genetic studies have shown that a

poly (U/UC) tract of at least_25 nt as well as the complete X-tail are required for RNA replication in cell culture and for infectivity of the viral genome in vivo.

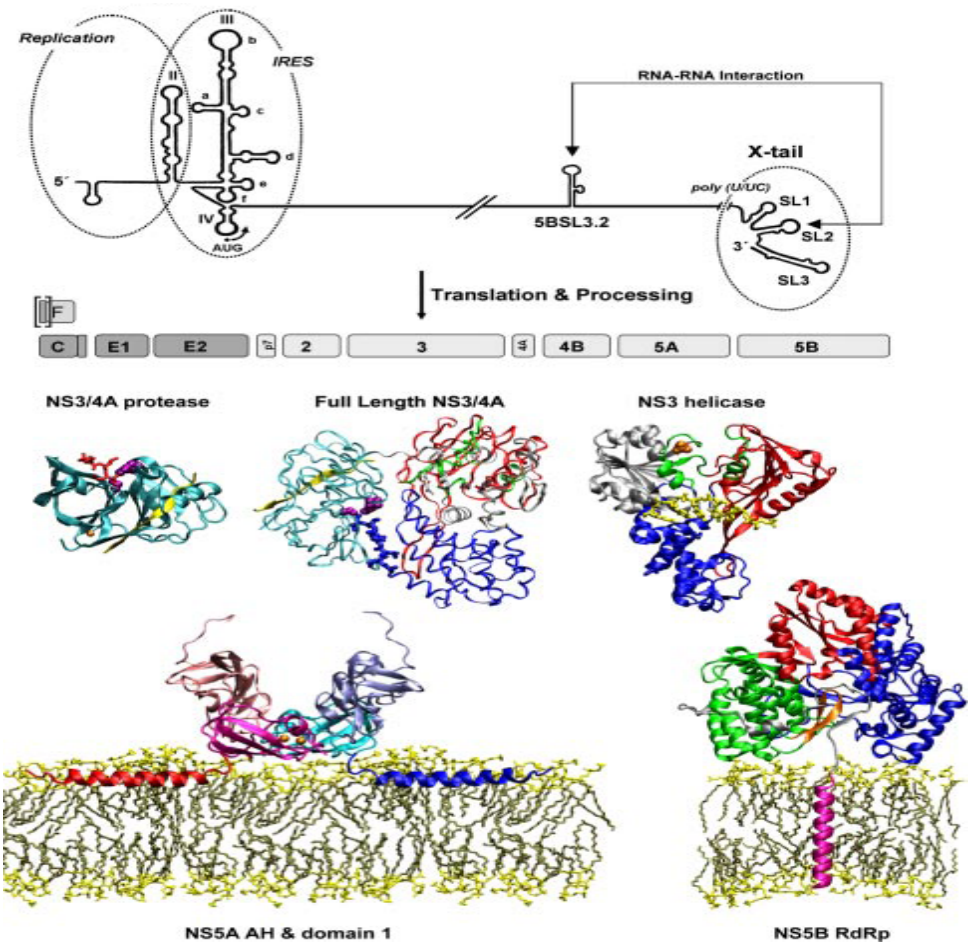

Figure (I): Aschematic of the HCV genome ***(Bartenschlager et al., 2004)***.

An additional cis-acting RNA element (CRE) has been identified in the 3_-terminal coding region of NS5B (Fig. I). This CRE (designated 5BSL3.2) ***(You et al., 2004)*** forms a long distance RNA-RNA interaction with SL2 in the X-tail ***(Friebe et al., 2005),*** which is indispensable for RNA replication.

Expression of the viral proteins from the monocistronic genome is primarily achieved by production of a polyprotein that is proteolytically cleaved into the structural proteins (core, envelope proteins E1 and E2), the hydrophobic peptide p7, and the non-structural (NS) proteins NS2, NS3, NS4A, NS4B, NS5A, and NS5B (Fig. I) ***(Penin et al., 2004).***

Processing of the core to p7 region is mediated by host cell signals, and in the case of the core protein, in addition by signal peptide peptidase. All remaining cleavages are carried out by two viral proteases: the NS2/3 protease mediating cleavage between NS2 and NS3 and the NS3 serine-type protease that is responsible for processing at all other sites in the NS polyprotein region.

Alternative forms of the core protein generated by internal initiation of translation of an alternative reading frame or by ribosomal frame shifting have been reported ***(Branch et al., 2005).*** These proteins designated ARF-P or F-proteins (for "alternative reading frame" or "frameshift") are dispensable for RNA replication, at least in cell culture.

Mode of transmission of HCV:

Prevention of infection remains the surest way to prevent HCV related complications and has other benefits including reduced risks for transmission of hepatitis B virus and HIV. There are three major modes of HCV transmission that need to be addressed: unsafe practices related to healthcare delivery, unscreened blood transfusion, and injection of illicit drugs ***(Shepard et al., 2005).***

Effort to address these issues in many developing countries including Egypt are underway but the costs associated with the procurement and proper disposal of single use syringes and other disposable devices pose an obstacle ***(Lohiniva et al., 2005).*** Transmission of HCV and other viruses from unscreened blood used for transfusion also remains a worldwide concern ***(Shepard et al., 2005).***

In developed countries, routine screening and testing procedures have virtually eliminated this risk. In developing world settings, transfusions have been relatively uncommon but as their use increases, it is critical that volunteer-based blood donation systems that include screening for blood born viruses be implemented. However, the infrastructure needed to support such systems can be expensive to develop and maintain. And blood safety is not always recognized as a high priority. Finally, injection drug use is the primary mode of HCV transmission in developed countries ***(Shepared et al., 2005).***

Although most of the patients who were through to acquire their infection through blood transfusion, many outbreaks that appeared not to be transfusion related ***(Hagan et al., 2001).***

Parenteral transmission of HCV:

1- Transfusion of blood or blood products:

Transfusion of blood or blood products was through to be the predominant route of transmission ***(Davis et al., 1993).***

Recipient of multiple transfusions are particularly at high risk, for example, patients with transfusion-dependent hemolytic disorders ***(Resti et al., 1992).***

Patients with hemophilia who were heavily transfused with non-treated factor concentrates have prevalence rate of anti-HCV exceeding 90% which higher than others ***(Tedder et al., 1991).***

In Egypt ***(Abdel-Wahab et al., 1994),*** reported prevalence rates of anti-HCV positively up to 54.9% of hospitalized multi-transfused children.

2- Hemodialysis:

HCV infection is common in patients on dialysis. In the past, the infection accounted for three-quarters of the acute hepatitis cases in hemodialysis units, and chronic hepatitis was common ***(Zeldis et al., 1990).***

Although most cases of hepatitis C in hemodialysis patients have been acquired through blood transfusion, outbreaks that are not transfusion-related have also been reported. But the exact mechanism of viral transfer remains elusive ***(Niu et al., 1992).*** The prevalence of anti-HCV antibodies in haemodialysis patients ranges from 10-30 ***(Touzet et al., 2000).***

3- Intravenous drug abuse:

The incidence of HCV infection among population of Intravenous drug abuser ranges from 4.2-22 per 100 person/years ***(Hagan et al., 2001),*** and the estimates of prevalence are between 30% and 90% ***(Van Ameijden et al., 1999).***

4- Transplantation:

HCV is transmitted by organ transplantation from anti-HCV positive donors, and up to 48% of recipients of organs from anti-HCV positive donors develop post-transplantation hepatitis C ***(Pereira et al., 1991).*** Due to immunosuppressant, detectable anti-HCV antibodies may develop in only 60% of infected recipients but HCV-RNA was detected in up to 96% of them ***(Pereira et al., 1995).***

5- Dental procedures:

Dentists are at risk of acquiring HCV, presumably from the blood and saliva of their patients. Oral surgeons are at particular risk ***(Klein et al., 1991).*** Infected tools can transmit HCV to patients ***(Esteban et al., 1996).***

6- Health care occupation:

Health care workers have an increased risk of acquiring HCV infection. Seroprevalence studies have reported an average anti-HCV rate of 1% among hospital-based health care workers ***(Pereira et al., 1995).***

Occupational transmission has been well documented but is thought to be rare. Prospective studies in health care workers after occupational exposure have documented transmission only after needle stick injuries with contaminated needles ***(Alter, 2002).***

7- Other potential transmission:

Other percutaneous exposures do occur such as tattooing, acupuncture and body piercing ***(Bartolotti et al., 1998).***

Non-parentral transmission of HCV:

They account for about 50% of cases of HCV infection as reported by ***(Alter et al., 1990);*** it includes sexual transmission, Vertical transmission and unapparent causes.

1- Sexual transmission:

Different studies were performed to determine the risk of sexual partner of anti-HCV positive patients for acquiring HCV infection. Sexual transmission is a documented mode of infection that accounts for a minority of cases of HCV. The precise risk of transmission is debated but is generally accepted to be less than 5%. The risk of acquiring HCV from sexual activity remains controversial ***(Alter, et al., 2002).***

2- Vertical transmission:

Vertical transmission is considered to be infrequent passive transfer of anti-HCV from the mother to baby occurs at the time of birth but infection of the neonate is much less likely. Both serological surveys and studies fail to document efficient

transmission of sustained infection, thus although anti- HCV and even HCV- RNA can be documented shortly after birth in babies born to mothers with HCV infection, these exposures are rarely associated with chronic infection ***(Reinus et al., 1992).***

An important observation linked transmission to the level of viremia. No maternal-fetal transmission occurred a among babies born to mothers whose HCV-RNA levels were less than 10^6 Copies/ ml while efficiency of transmission was as high as 36% if circulating levels of HCV-RNA$\geq 10^6$ Copies/ ml ***(Ohto et al., 1994).***

The risk of vertical transmission has been proven but is also difficult to quantify with estimates in the range of 6% in babies born to mothers with anti-HCV and 10% in babies born to mothers with HCV RNA. The prevalence of HCV in otherwise healthy children not known but is much lower than that in adults. Several investigators have reported a relatively high efficiency of vertical mother-to-infant transmission of HCV in mothers co infected with HIV ***(Zein et al., 2003).***

Data collected to date show no increase of HCV infection among breast fed babies; therefore breast feeding is not discouraged for mother with chronic hepatitis C ***(Manzini et al., 1995).***

Maternal history of chronic liver disease, mode of delivery and type of feeding are not predictive of HCV infection of the baby ***(Zanetti et al., 1998).***

3- Intrafamilial transmission:

It is still controversial whether the family environment plays role in the diffusion of HCV infection with variable incidence of transmission of HCV in non-sexual household contacts. Some studies failed to document interfamilial transmission ***(Ever hart et al., 1990; Puoti et al., 1995).***

In contrast, ***(Kiyosawa et al., 1994)*** reported an incidence of 8% of contacts to be seropositive. In Egypt ***(Abdel-Ghaffar et al., 1998)*** supported the possible interfamilial transmission.

Sharing of items such combs, razors, toothbrushes and nail scissors was proposed as means of unapparent potential transmission in non-sexual exposed family members ***(Grieco et al., 1998).***

4- Nosocomial transmission:

Allander et al. (1995) reported frequent patient-to-patient transmission of HCV in hematology ward.

Schvarez et al. (1995) suggested that failure of hygienic routines was a cause of outbreaks of HCV infection among hospitalized patients.

5- Other modes of transmission:

Chang et al. (1994) detected HCV genome in body fluid such as ascites, saliva, and urine.

Chen et al. (1995) reported that HCV is present in saliva in less than 25% of HCV viraemic patients.

The tear fluid contains HCV-RNA and may play role in HCV transmission ***(Feucht et al., 1995).***