

# **PREDICTION OF SUSTAINED VIRAL RESPONSE IN CHRONIC HCV PATIENTS TREATED WITH PEGYLATED INTERFERON AND RIBAVIRIN**

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## LIST OF ABBREVIATIONS

|                |                                         |
|----------------|-----------------------------------------|
| f A:           | in liver biopsy: grade of activity.     |
| f AFP:         | Alpha fetoprotein.                      |
| f ALP:         | Alkaline phosphatase.                   |
| f ALT:         | Alanine aminotransferase.               |
| f ANC:         | Absolute neutrophil count               |
| f ANA:         | Anti-nuclear antibody.                  |
| f AST:         | Aspartate aminotransferase.             |
| f b-DNA:       | Branched deoxyribonucleic acid.         |
| f BMI:         | Body mass index                         |
| f BUN:         | Blood urea nitrogen.                    |
| f B.W:         | Body weight.                            |
| f CBC:         | Complete blood count.                   |
| f cEVR:        | Complete Early virologic response.      |
| f CHC:         | Chronic Hepatitis C Infection           |
| f COPD:        | Chronic obstructive pulmonary diseases. |
| f CT:          | Computered tomography.                  |
| f DM:          | Diabetes mellitus.                      |
| f DVR:         | Delayed virological response            |
| f ECG:         | Echocardiogram.                         |
| f EDHS:        | Egyptian Demographic Health Survey      |
| f EIA:         | Enzyme immunoassay.                     |
| f eRVR:        | Extended Rapid virologic response.      |
| f ETVR or ETR: | End of treatment viral response.        |
| f EVR:         | Early virologic response.               |
| f F:           | in liver biopsy: stage of fibrosis      |
| f FBS:         | Fasting blood sugar.                    |
| f FDA:         | US Food and Drug Administration.        |
| f Fig.:        | Figure.                                 |

## **Introduction**

HCV is considered a major public health problem since the successful isolation and identification of its genome in 1989 (**Choo; et al 1989**). It is one of the most important causes of chronic liver diseases all over the world. It is estimated that approximately 170–200 million individuals are chronically infected with HCV, with about 3-4 million people are newly infected annually (**Lavanchy 2009**).

HCV is classified on the basis of their nucleotide sequence similarities into six major genotypes and many subtypes (**Simmonds, et al 2005 and Ramia, et al 2006**). The different genotypes have different geographic distributions with different effects on the response to interferon alpha treatment (**Rothman, et al 2005; Farci, et al 2006 and Morishima, et al 2006**).

Egypt has higher rates of HCV than neighboring countries as well as other countries in the world with comparable socioeconomic and hygienic conditions (**Kamal, et al 2008**). The recent Egyptian Demographic Health Survey [EDHS]; tested a representative sample of the entire country for HCV-Abs showed that, the overall prevalence of positive HCV-Abs was 14.7% (**El-Zanaty, et al 2009**). Approximately 90% of Egyptian HCV isolates belong to a single subtype 4a, which responds less successfully to interferon therapy than other subtypes (**Kamal, et al 2000 and Genovese, et al 2005**).

The primary goal of treatment for chronic hepatitis C (CHC) is to obtain a sustained virological response (SVR) which is defined as undetectable HCV-RNA, six months after completing the treatment. Long-term follow-up studies have shown that 97-100% of sustained responders retain undetectable HCV-RNA in serum and, in many cases, also in liver and peripheral blood mononuclear cells; strongly suggesting that SVR is associated with eradication of HCV infection. SVR can be also attained, even if at lower rates, in patients with extensive fibrosis or cirrhosis, decreasing the risk of HCC development and improving the overall survival rates (**Morgan, et al 2010; Backus, et al 2011 & Kanwal, et al 2011**).

According to all consensus guidelines (**AASLD 2009, NICE 2010 and EASL 2011**), the current standard of care (SoC) for CHC is the combination of pegylated interferon-alpha and ribavirin. For patients with HCV genotype 4, administration of this combined treatment for 48 weeks is associated with SVR rates of about 65%, and appears to be the optimal regimen, as concluded in a meta-analysis of six randomized trials (**Khuroo, et al 2004**).

Unfortunately, this combined therapy has a challenging side effect profile that necessitates prematurely stopping treatment in approximately 15% of patients & dose reduction in another 20-40% and thus affecting response rates. At the same time, this drug regimen is very costly to be afforded for a 48-week course. So, many efforts have been made to explore shorter but effective treatment durations (**Fried, et al 2002 and Davis, et al 2003**).

There are many host & viral factors, either pre-treatment or on-treatment, that are evaluated to assess their predictive role for SVR, and in this field, a number of studies have carried out to assess the role of the predictive power of early viral kinetics in assessing SVR (***Neumann, et al 2000***).

## **Aim of the work**

The aim of the work is to predict SVR in chronic HCV patients treated with pegylated interferon plus ribavirin depending on the following factors:

- Baseline viral load.
- Rapid viral response (RVR){at week 4 of treatment}.
- Very early viral response (VEVR){at week 8 of treatment}.

## **CHAPTER 1**

### **HEPATITIS "C" VIRUS**

#### **Background:**

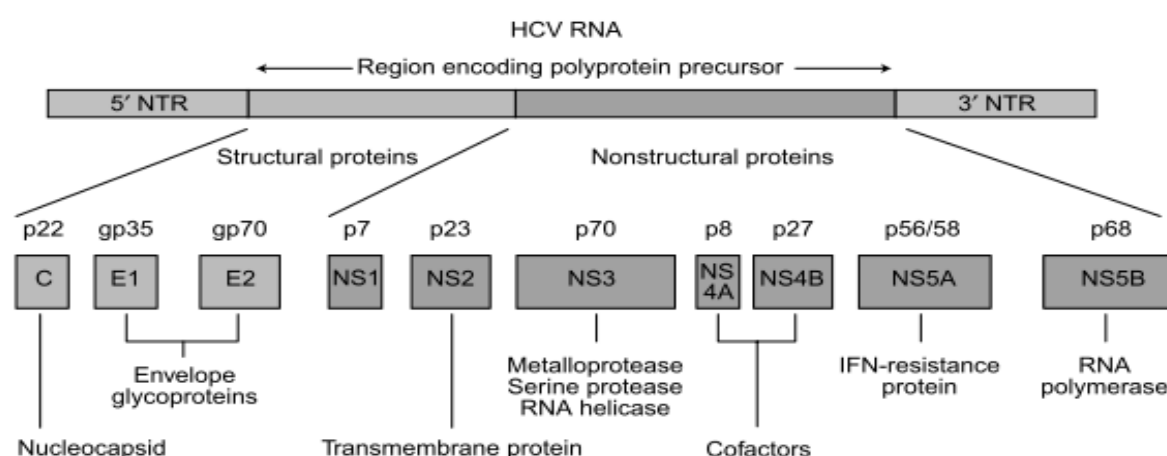
It became apparent after the discovery of hepatitis A and B viruses in the late 1960s and early 1970s that a large proportion of cases of acute and chronic hepatitis could not be explained by either of these agents, so another viral agent was suspected and patients infected with it were said to have non-A, non-B hepatitis. Every conventional method is used to isolate previous viruses had failed to detect this virus until 1989; when a group of researchers at the Chiron Corporation successfully cloning its genome by using the PCR, and designated it as hepatitis C virus (**Choo; et al 1989**). After that; many reports from the USA, Europe and Japan were rapidly issued characterizing the entire HCV genome and determining the viral proteins produced by HCV, the rudiments of viral replication and the extent of viral diversity in different regions of the world (**Choo; et al 1991 and Takamizawa; et al 1991**).

#### **Structure of HCV:**

HCV is belonging to the flaviviridae family and is the sole member of the genus hepacivirus. It is not related to any of the other known hepatitis viruses except HGV; which is a distant relative (**Büchen 2003**).

The reservoir of HCV is man, but the virus has been transmitted experimentally to chimpanzees (**Walker 1999**).

HCV is a small (40-60 nanometers in diameter), single-stranded positive-sense RNA virus, enclosed in a capsid shell and surrounded by a viral envelope (**Büchen 2003**). It has a genome of nearly 9.6 kb that encodes a single large open reading frame (ORF) that yields ~ 3000 amino acids and yields 10 main viral proteins. These proteins are classified as either **structural N-terminal proteins**; including the core (C), which forms the viral nucleocapsid, and the envelope glycoproteins E1 and E2 which are incorporated into new virions or **nonstructural (NS) C-terminal proteins**. The nonstructural (NS) proteins NS2 to NS5B are involved in polyprotein processing and viral replication (**Suzuki, et al 2007**), as shown in figure (1). The ORF is flanked by 5' and 3' untranslated regions (UTR), both 5' and 3' UTR bear highly conserved RNA structures, where the 5'UTR contains an internal ribosome entry site (IRES) that binds the 40S ribosomal subunit and initiates polyprotein translation (in a cap-independent manner), thus essential for genome replication (**Kolykhalov, et al 2000 and Suzuki, et al 2007**).



**Fig (1) “Model structure and genome organization of HCV”**  
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