UPDATED MANAGEMENT OF HEPATITIS C VIRUS DISEASES IN EGYPT

Essay

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in Internal Medicine

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List of Abbreviations

AICAR.....: ٥-amino-١-β-D-ribofuranosyl-imidazole-٤-carboxamide

ALT.....: Alanine aminotransferase

AKR.....: Aldoketoreductase

ART.....: Antiretroviral therapy

AST .....: Aspartate aminotransferase

AUC .....: Area under the curve

BMI.....: Body mass index

BOC .....: Bocepriver

Cmax.....: Maximum concentration

C min.....: Minimum concentration

CD٨١ .....: Cluster of Differentiation ٨١

CID.....: Chimpanzee infectious doses

CLDN.....: Claudin-١

CMV .....: Cytomegalovirus

CREs.....: Cis-acting replication elements

CTLs .....: Cytotoxic T-lymphocytes

D٢.....: Domain ٢

DCs.....: Dendritic cells

DGL .....: Deglycyrrhizinated licorice

E١.....: Envelop protein ١

E٢.....: Envelop protein٢

EGFR.....: Epidermal growth factor receptor

EIA.....: Enzyme immune assay

EMCV.....: Encephalomyocarditis virus

ESR .....: Estrogen receptor

EVR.....: Early virologic reponse

List of Abbreviations (Cont…)

FUSE.....: Far-upstream element

FXR.....: Farnesoid X receptor

GGT.....: Gamma glutamyltransferase

GWAS.....: Genome-wide association study

HCV.....: Hepatitis C virus

HCVCC.....: Hepatitis C virus cell culture

HDL.....: High density lipoprotein

HOMA.....: Homeostasis model assessment

HSV.....: Herpes simplex virus

Huh٧.....: Human "hemochromatotic" cell line

Hvap.....: Human vesicle-associated membrane protein

IL-٢٨.....: Interleukin ٢٨

IRES.....: Internal ribosomal entry site

IRF.....: Interferon-regulatory factor

IPS.....: Interferon promoter stimulator

ISGF.....: Interferon-stimulated gene factor

kcz.....: Ketoconazole

LDL.....: Low density lipoprotein

LDS.....: Lipid droplets

MHC.....: Major histocompatibility complex

miR.....: microRNAs

MTP.....: Microsomal triglyceride protein

NK.....: Natural killer

NTRs.....: Non translated RNA segments

OCLN.....: Occludin

ORF.....: Open reading frame

List of Abbreviations (Cont…)

PCR.....: Polymerase chain reaction

PEG -INF.....: Pegylated interferon

PPAR.....: Peroxisome proliferator-activated receptor

RBV.....: Ribavirin

RGT.....: Response guided therapy

RIBA.....: Recombinant immunoblot assay

RIG.....: Retinoic acid inducible gene

ROS.....: Reactive oxygen species

RVR.....: Rapid virological response

SGOT.....: Serum glutamic-oxaloacetic transaminase

SGPT.....: Serum glutamic pyruvic transaminase

SNMC.....: Neo-Minophagen C

SNP.....: Single nucleotide polymorphism

SOC.....: Standard of care

SOCS.....: Suppressor of cytokine signaling

SVR.....: Sustained virological response

TLRs.....: Toll-like receptors

TMA.....: Transcription-mediated nucleic acid amplification assay.

TNF.....: Tumor necrosis factor

TRIF.....: Toll/IL-\R domain-containing adapter-inducing IFN

TVR.....: Telaprevir

UTR.....: Untranslated region

VKH.....: Vogt-Koyanagi-Harada

VLDL.....: Very low density lipoprotein

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INTRODUCTION

Hepatitis is the Latin word for liver inflammation. Type C hepatitis is caused by hepatitis C virus, which is a small (٥٥-٦٥ mm), enveloped, single-stranded, positive sense RNA virus ***(Ryan and Ray, ٢٠٠٤).***

HCV virus is divided into the following genotypes: (١, ٢…. &١١).They are further divided into sub-types some of which are: (A, B, C … ect) ***(Westin et al., ٢٠٠٢).***

HCV is the most common leading cause of chronic liver disease, cirrhosis & hepatocellular carcinoma, as well as the most common indication for liver transplantation in many countries ***(Romero-Gomez et al., ٢٠٠٥).***

The worldwide reservoir of chronically infected persons is estimated at about ١٨٠ million, or ٣٪ of the global population ***(Wasley and Alter. ٢٠٠٠).***

Egypt has the highest HCV seroprevalnce in the world estimated at ١٥-١٧٪ of the country's population. Most cases of HCV are due to genotype ٤ viruses, which are uncommon in the west and understudied ***(Mohamed. ٢٠٠٤).***

The major known risk factors associated with HCV infection in Egypt are: past history of anti-schistosomal injections, circumcision, or other procedures performed by non-medical personnel, transfusion of blood, birth to an infected

mother, and intranasal cocaine use. Symptoms of acute hepatitis C infection include: loss of appetite, fatigue, abdominal pain, jaundice, itching, & flu-like symptoms & about ٦٠-٧٠٪ of patients are asymptomatic during the acute phase. Hepatitis C genotypes ٢A&٣A have the highest cure rates at ٨١٪ and ٧٤٪ respectively. While in chronic hepatitis C infection, it is often asymptomatic and is mostly discovered accidentally, and so blood test before marriage or any sexual contacts is essential ***(Caruntu and Benea, ٢٠٠٦).***

Interferon, which is an immune modulator, was the first medication approved for the treatment of hepatitis C virus; in ١٩٩٦ came the next improvement with the addition of Ribavirin. Early treatment of acute hepatitis C with Interferon monotherapy (pegylated interferon alfa-٢b) is highly effective, producing sustained virological response rates of ٨٥٪ or higher ***(Deterding et al., ٢٠٠٩).***

Recently, combination with Ribavirin, a greater number of patients are able to clear the virus ***(Herrera and Roveda, ١٩٩٩).***

The PROVE١ study demonstrated that addition of Telaprevir to the current treatment regimen improved virologic response to HCV ***(McHutchison et al., ٢٠٠٩).***

Also the use of Albumin interferon gives good results when used every ٢ weeks in combination with Ribavirin. ***(Davis et al., ٢٠٠٢).***

New research finds the anti-diabetic drug Metformin, and **AICAR**, can prevent the hepatitis C virus from replicating in the body ***(Richard Ashby, ٢٠١٠)***.

Herbal use such as milk thistle& tea made with licorice may help protect the liver from the dramatic effects of the virus. ***(Gazák et al., ٢٠٠٧).***

Liver transplantation is the last chance for someone whose hepatitis C has progressed to end stage liver disease ***(Schuppan and Afdhal, ٢٠٠٨).***

HCV vaccine:

In spite that there are vaccinations for hepatitis A&B viruses, the hepatitis C virus still has no vaccinations till now &researches are still going on to find one ***(Jacobson et al., ٢٠١٠).***

AIM OF THE WORK

The aim of the work is to review & discuss the new trends &drugs available in managing hepatitis C virus diseases.

MOLECULAR BIOLOGY OF HEPATITIS C VIRUS

In the ١٩٨٠'s, investigators from the Centers for Disease Control (headed up by Daniel W. Bradley) and Chiron (Michael Houghton) identified HCV, which is a small (٥٥ - ٦٥ nm), spherical, enveloped, hepatotropic RNA virus prototype, member of the Flaviviridae family, the Hepacivirus genus (from the Greek hepar, hepatos, liver) is further classified into genotypes that differ by about ٣٠٪ in their nucleotide sequence. These genotypes (١, ٢, ٣…, ١١) show differences with regard to their worldwide distributions, transmission & disease; they have been further classified into sub-types (a, b, c, d, etc). (Fig. ١) ***(Thein and Dore, ٢٠٠٩)***

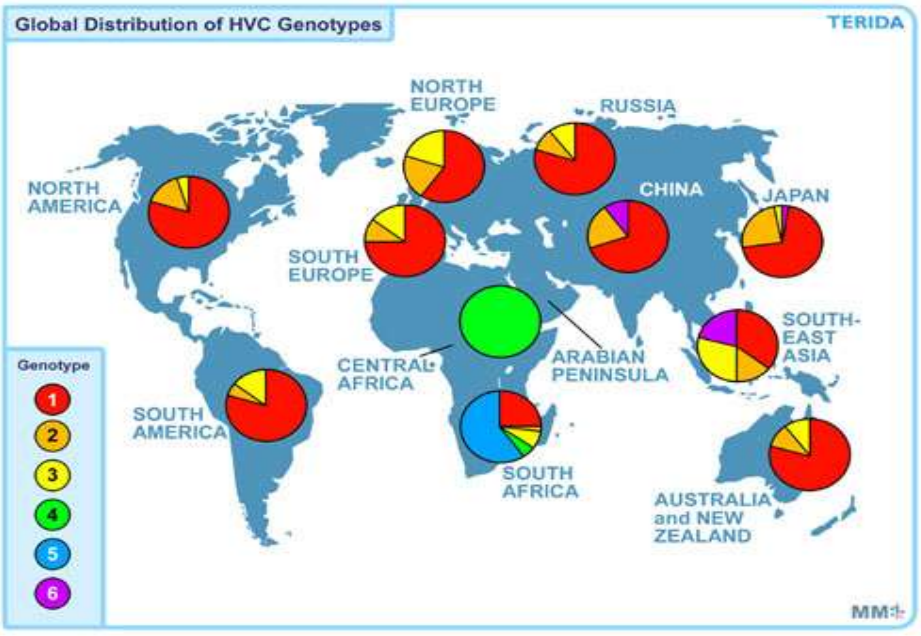

Fig. (١): Global distribution of HCV.

HCV type ٤ virus is the dominating virus found throughout The Middle East and parts of Africa, often in Egypt. Molecular studies of HCV began with the successful cloning of its genome in ١٩٨٩ ***(Kuiken et al., ٢٠٠٩).***

Even though HCV is detected and targeted by host immune mechanisms, it establishes and maintains a life-long persistent infection. HCV has evolved multiple strategies to survive and persist in hostile cellular environments, and the viral population is known to rapidly change during the course of a natural infection thereby escaping immune surveillance ***(Von Hahn et al., ٢٠٠٧).***

Although precise mechanisms regulating HCV entry into hepatic cells via receptors remain unknown, HCV also has the capability of direct cell-to-cell transmission. The extremely complex and incompletely understood nature of the HCV lifecycle has complicated the discovery of new therapies ***(Diviney et al., ٢٠٠٨).***

A break through in the field came with the development of a complete in vitro cell culture system for HCV (JFH١) in ٢٠٠٥ ***(Wakita et al., ٢٠٠٥).***

Present inside the outer envelope, there is a (٣٠-٣٥ nm) inner core which encapsulates the single-strand viral RNA (positive-sense), which is approximately ٩,٦ kb (Fig.٢).

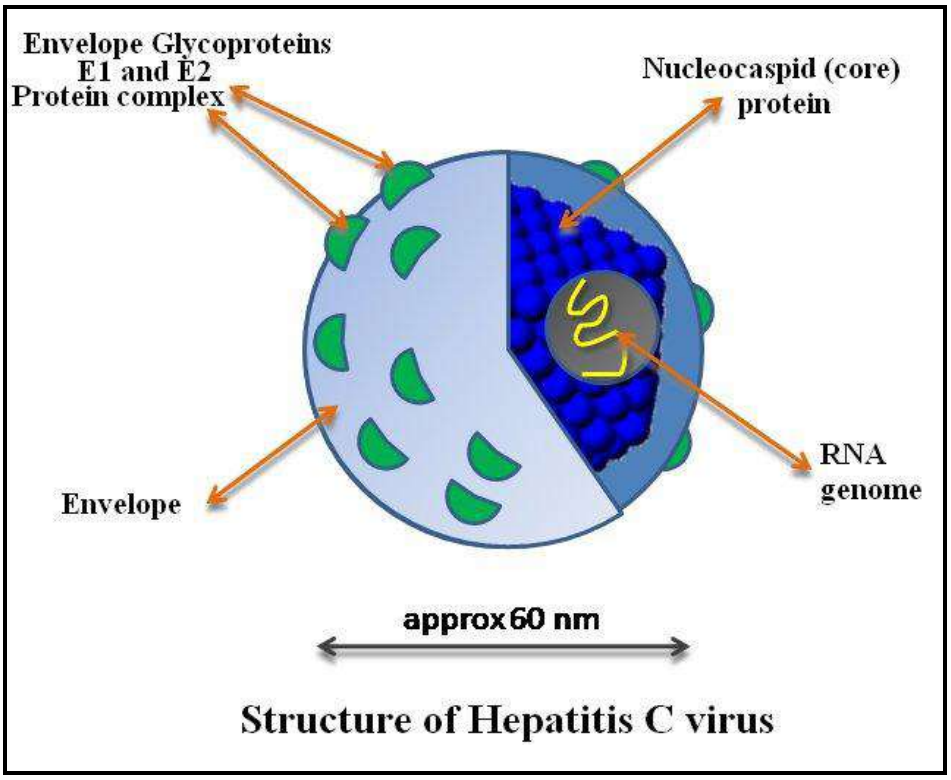

Fig. (٢): HCV particle structure: core protein Interacts with viral genomic RNA to form the nucleocapsid. Two membrane-associated envelope glycoproteins, E١ and E٢ are embedded in a lipid envelope which is derived from the host ***(Cheng et al., ٢٠٠٩).***

The HCV genome does not enter the cell nucleus. HCV-RNA replication occurs in the cytoplasm of hepatocytes. The genomic organization of HCV is shown schematically in **Fig. ٣**.

The viral-RNA genome harbors a single ORF which is iflanked by ٥' and ٣' NTRs. The CREs are located in both the ٥' and ٣' NTRs and in the NS٥B coding sequence ***(Diviney et al., ٢٠٠٨).***

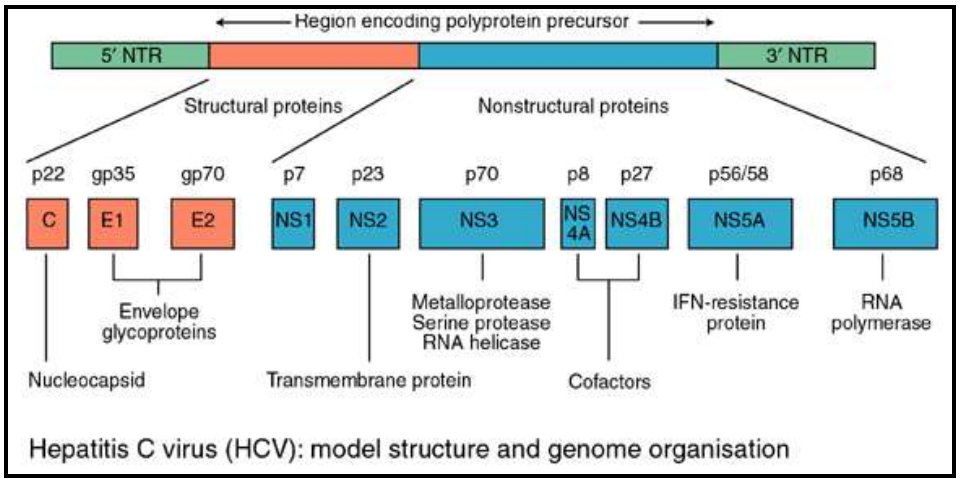

Fig. (٣): The genome consists of a single ORF which is translated to produce a single protein product .At the ٥' and ٣' ends of the RNA are the UTR, which are important to translation and replication of the viral RNA. The ٥' UTR has IRES that starts the translation of a very long protein of about ٣،٠٠٠ amino acids. Structural proteins made by the hepatitis C virus include Core protein, E١ and E٢; nonstructural proteins include NS٢, NS٣, NS٤, NS٤A, NS٤B, NS٥, NS٥A, and NS٥B. *(Dubuisson J, ٢٠٠١)*

This CRE is called as SL٩٢٦٦ (or ٥BSL٣,٢) and it was found that its disruption blocks RNA replication ***(Friebe et al., ٢٠٠٥).***

The ٥'- and the ٣'-NTRs of the genome are highly conserved and contain control elements for translation of the viral polyprotein and replication. The ٥′ UTR contains IRES which is required for cap-independent translation of viral RNA, which is carried out by host cell ribosome ***(Shimoike et al., ٢٠٠٩).***

A recent study identified a cellular factor called FUSEbinding protein FBP which binds to ٣'NTR by interacting with the poly (U) tract ***(Zhang et al., ٢٠٠٨).***