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HEPATITIS C VIRUS: AN OUTLINED REVIEW

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ABSTRACT: Chronic hepatitis C (CHC) is a big cause of liver-related fibrosis and cirrhosis. The level of fibrosis is usually in the past (established by histology). The prognosis is estimated using fibrosis progression rates (FPRs; the annual probability of progressing across histological stages). However, new non-invasive options are quickly replacing biopsy. As the rates of HCV cirrhosis go on increasing and hence remains high, the morbidity and mortality of HCV- related HCC. Reduced complications from cirrhosis, including HCC, is one of the long term goals of antiviral. The new directly acting antiviral development with high rates of virological clearance has restructured the cure of HCV infection. Fewer patients remain at risk for hepatocellular carcinoma, especially those with the severe fibrosis and cirrhosis in spite of the development of HCC in HCV patients who achieve disease sustained virologic response is reduced. This review puts lights upon the overview, morphogenesis, infection, therapies. The discussion outlined will be helpful to the chemist and learners of the exact mechanism and set the broad spectrum identification of creative anti-HCV compounds. The prime objective of the review is to provide insights on HCV medicinal chemistry. In spite of promising significant advances, noteworthy difficulties stay for reducing HCV-related morbidity and mortality.

Keywords:

Antiviral agents, Hepatitis, Hepatocytoprotective, Fibrosis

INTRODUCTION: Hepatitis is one of the most serious diseases in the world. The biggest organ in the human body is the liver affected by this disease. It has an area in the upper right of midriff and about the size of a football. We can't live without the working of the liver. It is the warehouse and body's filter. It can have a serious impact on human working when something turns out badly as practically all tissues and cells rely upon the liver.

The level of certain substances in the body is regulated by the liver like fats, hormones, and carbohydrates, which are essential for survival and are potentially harmful when out of balance. An essential role of the liver is digesting food since it processes the formation of bile. The blood-clotting factor is controlled by the liver, which counteracts uncontrolled bleeding. Inflammation (swelling) of the liver is eluded as hepatitis.

The ancient greek word hepa alludes to the liver, and it implies swelling (as in joint pain, dermatitis, and pancreatitis) [1]. Exposure to poisons and chemicals, for example, an excessive amount of liquor, an abnormal immune response to healthy assault tissues in the body, fat which may lead to build-up of fat in liver disease, microbes, including viruses, is a significant reason for hepatitis. A hepatocyte is the main tissue of the liver. Hepatocytes make up 70-85% of the liver's cytoplasmic mass. It gives the best conditions to these viruses like HAV, HBV, and HCV to replicate. As a reaction to this infection, the body's immune

system targets the liver, which causes Swelling (hepatitis). On the off chance that where the inflammation is extreme (which can occur with HAV and HBV) or continues for a significant time period (which can occur with HBV and HCV), large amount of scar tissue in the liver, a condition is called as fibrosis. It occurs when the liver attempts to repair and replace damaged cells.

The normal flow of blood throughout the liver is blocked by formed hardened scared tissue instead of normal liver tissue and truly influences its structure and capacity to function legitimately after the long time infection because of this virus. This procedure is called cirrhosis. Blood gets accumulated into the spleen and the digestive organs if the liver is seriously harmed, causing increased tension in these organs [2]. This condition is called portal hypertension includes loss of blood and ascites (build-up of fluid in the abdomen). Significant liver harm diminishes the formation of bile required for correct digestion, and it can diminish the liver's capacity to store and process supplements required for survival. Liver damage affects the ability to remove toxins from the bloodstream, which can eventually lead to mental confusion and even coma (hepatic encephalopathy). There are five viruses that affect the liver and give rise to hepatitis: Hepatitis A virus, Hepatitis B virus, Hepatitis C virus, the delta hepatitis infection (HDV, which only causes problems for people infected with HBV) and hepatitis E infection (Hepatitis E virus). Most of the death occurs due to cirrhosis or liver cancer in men and women acquired with HBV and HCV infection [3, 4].

Although on average, globally, 84% of vaccines exist, vaccines are not always protective for infants whose mother has high viral loads. Even though several drug treatments are available as antiviral drugs for hepatitis B and C, but it is not available in a developing countries and not even cost-effective. To date, there is no vaccine reported for HCV as the genotype of virus observed in different areas is different. HCV virus exists at least in 6 distinct genetic forms (genotypes) with multiple subtypes. Almost 50 subtypes have been identified. A global vaccine to be developed so as to protect against all these variants of the virus. Even if several anti-viral drugs, including HuIFN-alpha-Le and nucleoside analog reverse transcriptase inhibitors, have been used for the hepatitis B treatment. Still, huge issues remain as including moderate efficacy, dose-related adverse effects, and drug effective due to resistance. Along these lines, the remarkable medical requirement for safe and effective anti- HCV drugs exists, and finding new anti-HCV agents remains a challenge [5, 6].

HCV is a tiny engulfed virus that has a single-stranded RNA genome, positive-sense that encodes a large polyprotein of 3010 amino acids. In order to form mature structural and non-structural (NS) proteins, the polyprotein is co- and post-translationally processed by cellular and virally encoded proteases. For viral maturation and replication, the NS3 serine-like protease enzyme and RNA- dependent RNA polymerase (RdRp) is essential [7-10].

Symptoms: Infection for longer period of time with the hepatitis C virus (HCV) is known as chronic hepatitis C. Signs, and symptoms of these infections are abnormal bleeding, contusion, Fatigue, loss of appetite, yellow pigmentation of the skin and eyes (jaundice), Dark urine, Itchy skin [11-13]. Fluid development in your stomach area, retention of fluid in leg tissues causing edema, reduced weight, disconcertion, sleep disorder and dysarthria, spider naevus.

Structure: HCV is an enveloped, positive-stranded RNA virus classified in hepavirus genus within Flaviviridae family. It has 7 genotypes, and HCV 84 subtypes currently recognized [14-18].

Life Cycle: HCV life cycle is tightly linked to the lipid metabolism of the hepatocyte. HCV utilizes the liver cell for its development. The virus is located with the protein-specific layer.

Locate and connect these proteins to an element called a receptor on the surface of liver cells. The receptor gets signals for liver cells. The virus reaches the external barrier of liver cells. Then, the barrier surrounds the virus picks it up and put it in the cell.

The coating of virus breaks down viral RNA carrier genetic information is propagated into a liver cells. Viral RNA is ready for reproduction. It imitates the RNA of liver cells and starts to make its RNA products. It can also inhibit the proper functioning of liver cells. Sometimes, the viral RNA also triggers the reproduction of liver. Things amplify as viral RNA builds a template to replicate itself. The virus replication mechanism is not fully grasped. Time and again,, viral RNA is cloned to produce fresh viruses. The coating of viruses consists of various protein-based coverings. These are created and released during this phase by ribosomes or cell proteins builders [19-21].

Capsomers (proteins units) come together and form new particles around the viral RNA. These create sphere-shaped coverings, called as a capsid. The virus's genetic material is protected by it. In the end stage, the virus produces a bud inside in the final phase. The bud is surrounded by a protective cover. It is propagated through the liver cell barrier, ready to infect another cell in the liver. This procedure goes on till the infected liver cells die. 9600 bases are there in the HCV genome, which is edged by 5' and 3' non-translated region as a continuous open reading frame. Internal ribosome entry site is essential to initiate the translation of the HCV genome at 5' non-translated region.

Approximately 3000 = 3300 amino acid polyprotein precursor is produced by the IRES-mediated translation process, which cleaves co subsequently and post-translationally into mature viral structural and non-structural proteins. Enzyme cellular peptidases and two viral proteases NS2/3 and NS3 cause proteolytic processing of polyproteins, which leads to break into 10 functional subunits like C, E1, E2, P7, NS2, NS3, NS4A, NS4B, NS5A, NS5B. Where C, E1, E2 subunits from virus particles in which nucleocapsid is nonstructural from repeated copies of core proteins (C) and E1, E2 form (glycoprotein) envelope. Assembly and release of virus particles is a function of P7. Virus replicate complex formed from NS Proteins [23-26]. Below is the figure of the HCV virus and its life cycle.

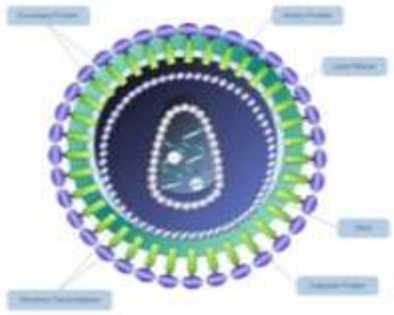

FIG. 1: DIAGRAM OF HCV VIRUS

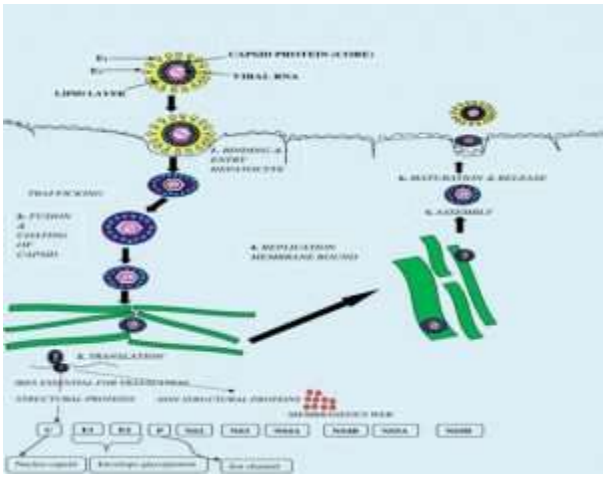

FIG. 2: HCV LIFE CYCLE; 1) BINDING & ENTRY 2) FUSION AND UNCOATING OF CAPSID 3) TRANSLATION 4) REPLICATION ON MEMBRANE BOUND 5) ASSEMBLY 6) TRANSPORT, MATURATION AND RELEASE

HCV Transmission Routes: Main route of HCV infection is blood and blood products. Transfusion of clotting factors, blood transfusion of unscreened products, organ transplantation, medical instrument reuse (like syringes, cathartics, needles, infusion sets), *etc.* may be the cause of HCV infection. Unsafe sex is but controversial.

Mother to child transmission, human immunodeficiency virus, co-infected mothers during normal delivery, C section are the HCV transmission modes. It is also seen that the use of tattoos, sharing razors, and acupuncture may cause infection. Casual household contact and contact with the saliva of those infected are inefficient modes of transmission [27-30].

Mode of Transmission: The essential mode of HCV transmission is a blood-borne transmission. Hazardous infusion hones in healthcare settings and recreational infusion medicate utilization are especially vital for HCV transmission around the world [31]. In joined together, states in 1992 earlier to the screening of blood items for HCV starting, the healthcare-associated transmission of HCV happened more habitually; in any case, 33 healthcare episodes including more than 239 outbreak-associated cases were detailed to the Centers for Illness Control and Avoidance [CDC] from 2008–2015 [72].

Vertical transmission can happen in ~6% of newborn children born to HCV-infected moms and transmission may be twice as likely to happen in newborn children born to HCV/HIV co-infected moms or HCV mono-infected moms with tall viral loads [32-36].

Sexual transmission is for the most part wasteful; in any case, an expanding number of cases of sexually transmitted disease have been detailed among HIV-infected men who have sex with men [MSM]. At last, HCV transmission has too been detailed within the setting of non-injection sedate use as well as within the setting of unregulated tattoos [37].

Testing and Diagnosis: Research facility determination of persistent HCV contamination within the Joined together States as of now requires the utilize of two sorts of tests: immunoglobulin (Ig) G antibody chemical immunoassays (anti-HCV) and nucleic acid tests (NAT). HCV testing ought to be started with an anti-HCV counteracting agent test [38]. People without hazard variables for HCV and a non-reactive anti-HCV counteracting agent require no advance assessment for HCV contamination. Additional testing may be suitable for certain populaces with seriously compromised resistant frameworks or current dangers for HCV introduction such as infusion sedate utilize or hemo dialysis [39]. A responsive anti-HCV counteracting agent

requires affirmation with an HCV NAT to decide the nearness of HCV RNA and current HCV contamination. People with a reactive anti-HCV antibody and a positive HCV NAT are infected with HCV and ought to be connected to suitable HCV therapeutic care and treatment [40]. Diagnostic: For HCV diagnosis, both serologic and nucleic acid-based tests were developed [41-48].

Serologic tests are adequate when constant hepatitis C is anticipated, with a sensitivity of more than 99% in case utilizing the 3rd generation assays. Positive serologic comes about require extra HCV RNA or (with somewhat decreased sensitivity) HCV center antigen estimations in arrange to distinguish between chronic hepatitis C and settled HCV disease from the past. When an acute hepatitis C is considered, a serologic screening alone is inadequate, since mature anti-HCV antibodies are developed late after transmission of the infection [49-51]. Because of low sensitivity, poor specificity, and low efficacy compared to serologic and nucleic acid-based approaches, morphological methods like immune histo-chemistry, in situ hybridization, or PCR from liver specimens does not play any relevant role. HCV core antigen assay: There are 5 different antibodies targeted the HCV core in the assay [52-56].

Diagnosis: Serologic Assays that detect human antibodies generated as a response to HCV infection is done in initial testing for the diagnosis of HCV infection. Laboratory diagnosis for the HCV infection test requires the use of 2 types of test- (IgG) antibody enzyme immunoassays nucleic acid test (NA) [57-65]. Diagnosis is recommended in those patients who have a high level of ALT. Amplification techniques such as polymerase chase reaction may be used to detect HCV RNA in blood. Depending upon the severity of the infection and its diagnosis, therapeutic decision making, assessment of virological response to therapy can be done.

The cost of new HCV core antigen assay method is low, in spite of the fact that, to some degree, less sensitive, elective for nucleic acid testing for HCV [66-67]. The early diagnosis of acute hepatitis C should be done and considered as mandatory as it is detectable in a few days of infection. The nucleic acid-based tests are available and are efficient [68].

The HCV RNA measurement is besides vital in determination of the HCV genotype, selection of treatment procedure, therapy duration, and assessment of the treatment success HCV RNA estimation. For a number of antiviral combination treatments, the HCV RNA follow-up thinks about are fundamental to characterize the result of the treatment and encourage helpful techniques, if vital [69].

Traditionally, in order to evaluate that a sustained virologic response (SVR) was achieved or not, the tests should be repeated until 24 wk after treatment completion. However, Now the 12 wk is the new time point for evaluation of the final outcome of virological treatment, and after the end-of-treatment, the interference of a virologic decadence is equal after 12 and 24 wk [70-75] and for the both qualitative as well as quantitative, PCR-based detection assays method are available. The initial diagnostic of hepatitis C is done using qualitative PCR tests being sensitive, and for a screening of blood, organ donations and for confirming SVR after treatment completion, qualitative PCR assays are used [76-78]. Quantitative reverse transcriptase (RT) real-time PCR-based assays can detect and quantify the HCV RNA over a very wide range, from approximately 10 IU/ml to 10 million IU/ml. In the treatment monitoring, when the virus load is gradually reducing, the measurements are essential [76, 77]. Identification of HCV genotyping is also a very important factor for the patients who are recommended for antiviral therapy. And for assessment of the HCV genotyping, both direct sequence analysis and reverse hybridization technology are used. The only drawback is that these methods do not assess the genome subtypes, and because of this drawback, currently assays were additionally analyzing the coding regions. Genes encoding core protein and the NS5B gives non-overlapping sequence differences between the genotypes and subtypes [78].

Treatment: Chronic HCV infected patient needs to be treated as early as possible.

i) If cirrhosis and fibrosis bridging is there in patients needs to be treated at earliest so as to avoid the propagation of cirrhosis.

ii) Liver transplant recipients should be treated.

iii) If any extrahepatic manifestations are there in patient need to be treated [79], *e.g.,* Porphyria cutaneatarda or glomerulonephritis- treatment is recommended.

In order to avoid the risk of transmission of disease during the delivery of the infant, women should be treated before being pregnant [80]. Treatment during pregnancy is not recommended. There are several antiviral drugs that can be used for the treatment of HCV infection. There have been made significant advances in treatment for HCV using new direct-acting antiviral medications, sometimes in combination with the existing ones [88-90]. HCV genotype, Severity of liver damage, other medical conditions, and prior treatment decide the choice of medications, length of treatments. WHO recommends treatment to all individuals diagnosed with HCV infection who are 12 years of age or older, irrespective of disease stage. Who recommends treatment to adolescents aged of 12-17 years, weighing 36 kg at least with HCV infection [81-83]. Now a day's medication prescribed is as given in **Table 2**.

A treatment regimen differs until 12 years of age. Treatment with interferon-based regimens should no longer be used

According to some randomized trial combination of interferon and Glycyrrhizin is more effective than single interferon therapy, which used in the treatment of chronic hepatitis c, and the patient in which single used interferon are ineffective [83].

CONCLUSION: HCV is infectious. The most common reason is unsafe injections, transmitted by percutaneous blood exposure. It seems to be endemic in most parts of the world. Long term complication of HCV infection includes cirrhosis and hepatocellular carcinoma. Fundamental studies on virus-cell interactions and studies directing towards the development of the prophylactic vaccine should be intensified. There are several advances in HCV treatment have created new opportunities for reducing HCV-associated morbidity and mortality. These treatments are safe, well-tolerated, and highly effective. However, the benefits cannot be realized without a significant increase in the number of persons tested for HCV so that all chronically infected individuals can be aware of their diagnosis and linked to appropriate clinical care.

ACKNOWLEDGEMENT: The author thanks DYPIPSR for providing the necessary facility to complete work.

CONFLICTS OF INTEREST: The author(s) confirms that there is no conflict of interest.

REFERENCES:

1. Ly KN, Hughes EM, Jiles RB and Holmberg SD: Rising mortality associated with hepatitis C virus in the United States, 2003-2013. Cli Infect Dis 2016; 62(10): 1287-8.
2. Allison RD, Tong X, Moorman AC, Ly KN, Rupp L, Xu F, Gordon SC and Holmberg SD: Chronic Hepatitis Cohort Study (CHeCS) Investigators. Increased incidence of cancer and cancer-related mortality among persons with chronic hepatitis C infection 2006-2010. Journal of Hepatology 2015; 63(4): 822-8.
3. AASLDI: HCV Guidance: Recommendations for Testing. Managing and Treating Hepatitis C 2016.
4. Smith BD, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Teo CG, Jewett A, Baack B, Rein DB, Patel N and Alter M: Recommendations for the identification of chronic hepatitis C virus infection among persons

born during 1945-1965. Morbidity and Mortality Weekly Report: Recommendations and Reports 2012; 61(4): 1-32.
5. Alter MJ and Margolis HS: Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease.
6. World Health Organization. http://www. who. int/ mediacentre/factsheets/fs340/en.
7. De Francesco R, Tomei L, Altamura S, Summa V, Migliaccio G. Approaching a new era for hepatitis C virus therapy: inhibitors of the NS3-4A serine protease and the NS5B RNA-dependent RNA polymerase. Antiviral Research 2003; 58(1): 1-6.
8. Beaulieu PL and Tsantrizos YS: Inhibitors of the HCV NS5B polymerase: new hope for the treatment of hepatitis C infections. Current Opinion in Investigational Drugs (London, England: 2000) 2004; 5(8): 838-50.