

DIAGNOSIS, TREATMENT AND COMPUTATIONAL APPROACHES: HEPATITIS-C

BATRA UNNATI¹, TRIPATHI MEGHNA², NAGARAJAN K*, JAGANNATH SAHOO⁴

KIET School of Pharmacy, KIET Group of Institution, Ghaziabad, Uttar Pradesh, India

*CORRESPONDING AUTHOR: Dr. Kandasamy Nagarajan, KIET School of Pharmacy, KIET Group of Institutions, Ghaziabad, Uttar Pradesh, India.

ABSTRACT

Hepatitis C viral infection is a major affecting liver disease most consistently found in users of drug by injection route. The transmission is attained by percutaneous or permucosal attainment to the blood infected with Hepatitis C viral infection. This type of infection occurs 20% acutely and around 70% chronically. The major concern for the disease is that it may or may not show any symptoms, fewer than half of those infected with HCV may be aware of their infection. Majorly this infection can be leading cause of hepatocellular carcinoma. clinical manifestations of HCV infection relate to various studies about HCV associated Hepatocellular carcinoma (secondary malignancies). The pathophysiology of the disease perfectly indicated the high

risks towards cirrhosis at later stages. The diagnosis of the disease is poorly screened as HCV RNA cannot be detected easily in the blood. this is called sustained virological response. In the recent past USFDA approved two new protease inhibitors for the treatment of the disease. The future aspects in the field of creating a treatment lead to various approaches of new drug discovery through computational procedures. The future aspects including all the diagnostic and treatment procedures for hepatitis c virus infection have been introduced in this review in the elaborated way, which is a more challenge in terms of innovation & sustainable development in the area of drug discovery against hepatitis-C infection.

KEYWORDS-Cirrhosis, Hepatitis C Virus, Hepatocellular Carcinoma, Protease Inhibitors

1. Introduction

Derris B. Stridersetal in United States, there are more than 2.7 million people who are affected with Hepatitis C virus (HCV) infection. Nowadays, the major health problem amongst the people is liver damage and, the cause of this is only HCV infection. The main aim of writing this article is to provide and spread the information amongst the people and to aware them regarding the HCV infection and its related terms. [1] The data given by MaxineDennison *etal* showed that between 2001 to 2008 people who had participated in National Health and Nutrition

Examination Survey (NHANES), only 49.7% were aware of their HCV infection although 85.9% heard of HCV. So,

these data indicate that more efforts should be taken to reduce the risk of HCV infection. [9]

Many symptoms like weariness exertion and also fatigue have been seen in the patients infected with HCV. According to some estimates approximately 3-4 million people get infected by HCV infection each year. [4,7] The transmission of HCV include exposure to infected blood or other blood derived body fluids, transportation of organs from infected person, reusing the used needles. To prevent the spread of HCV some strategies should be taken into

account like routine check-up, awareness camps, counselling of patients, usage of effective vaccines, etc. [5,7]

The diagnosis of HCV infection includes Anti-HCV tests, HCV RNA assays, HCV genotyping. Currently in USA the second generation enzyme immunoassay (EIA-2) is majorly playing an important role in diagnosis of HCV infection through Anti-HCV tests. Up to 60% of the patients with HCV 1 genotype infection do not have a sustained virological response to many drugs. Various studies have found that alcohol consumption increases the risk of having liver cirrhosis in patients ongoing HCV infection. [8,13] Currently the computer aided drug design is a most important and useful parameter in identification, optimization, and structure elucidation of candidate drugs. As HCV infection has become much more troublesome to handle, so with the help of computer aided drug designing we can design new drugs for curing HCV infection. [15]

2. Epidemiology

Hepatitis C virus is the virus which takes up the transmission route through the blood and comes as a sexually transmitted disease which actually incorporates a higher risks of occurrence in people with concurrent changing sex partners.(1) Also the transmittal tendency of the virus increases when the drug consumers are taking the drug through injection. This causes a high rate of outburst contact risking to the virus from percutaneous and permucosal which leads to cause of HCV(2,5). The global epidemiology of HCV is indicating the risk of HCV infection according to various areas related to different geographic. A study by Hanafiah M K *et al* stated that Central and East Asia have high prevalence of the disease, Caribbean, Oceania, Australia has moderate risk of disease occurrence and North America at a lower risk of occurrence. The lower prevalence area also includes the western Europe and Australia(5). The estimated global prevalence is around 3-5%, 170 million infected by HCV infection (18). Since the HCV have no symptoms all the time it is very important for the proper diagnosis of the disease, it should have correct medical follow ups among the people of society.(9). The population throughout the world is affected to chronic HCV infection in a number of 130-170 million around the world(11). The rates and number may vary with the different

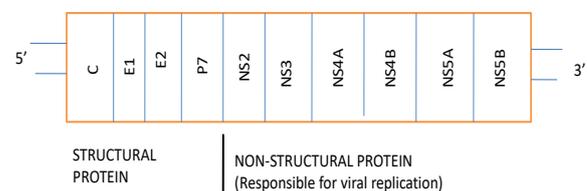
studies but high prevailing geographical area always incubates the disease causing virus. Throughout a good health care framing system it has been recommended for consecutive follow ups for the people among the injection users(15,2). A study also marked the statement that the number of persons with anti-HCV in worlds has increased from 1990 to 2005 (7).

3. Etiology and Pathophysiology

The causative agent of the HCV infection is the hepatitis c virus (HCV), although Anti-HCV therapies are there to treat the HCV infection but, the alliance of Ribavirin and interferon Alfa was the most effective care that is available, which was effective to only 60% of the population and showed its side effects to some extents. [25] Some characteristics of this infection include persistent infection with irregular biochemical infection, very less probability regarding sudden reoccurrence of the infection, very high probability to move to cirrhosis stage, and very less immunity to another infection. [17]

The role of stem cells and apoptosis was found to be the reason behind the pathogenesis. Councilman-like bodies was found to be present in HCV infection from decades. [18] The reasons that are responsible for the HCV infection are Hepatocellular Carcinoma, which further cause liver damage. [3]

OPEN READING FRAME OF HCV



C-Core C protein
 E1, E2- Envelope glycoprotein to form structural component of viral assembly
 P7- Ion channel for viral assembly
 NS2- protease for viral assembly
 NS3, NS4- Protease enzyme
 NS5A- Phosphoprotein
 NS5B- RNA dependent RNA polymerase

4. Clinical Manifestation

Usually the HCV infection do not provide any symptoms for the prevailing judgement of the disease(1,9). This includes the risks of prevalent of the disease to the later stages and the resultant may lead to various other effects like pain in the abdomen, gastrointestinal bleeding, swollen blood vessels seen through the skin also depression or weight loss. The further symptoms may also include yellowing of the eyes. Further stages of the HCV infection may lead to the liver cirrhosis which concludes the retardation of one part or multiple parts of the liver.(11, 14). Further studies have also reported the inclusiveness of hepatocellular carcinoma in the later and final stages of HCV infection Chronic Hepatitis C virus (HCV) infection is a leading cause of hepatocellular carcinoma (HCC) worldwide. Relative to the uninfected population, patients with HCV infection have an ~10- to 20-fold greater risk of HCC (10)

5. Diagnosis and Treatment

The HCV infection can be identified in more than 90% of cases. Clinically Anti-HCV tests and HCV-RNA assays are used to diagnose the HCV infection. The quantitative assays establish the quantity of HCV-RNA in the blood by two methods, either by target amplification or by single amplification technique. Through HCV-genotyping also, we can estimate the probability of occurrence of responses after the treatment, and also estimates the total time being required for the treatment to get completed. The Genotyping is performed either by polymorphism or by direct sequence analysis. [1]

Interferon Alfa and Ribavirin are majorly used for treating the HCV infection in patients who are currently injecting the illegal drugs, consuming alcohol, and also for the patients ongoing HCV infection with IUDs. [2] various tests like Anti-HCV tests, HCV RNA assays are being done to diagnose the HCV infection. For more prominent results, PCR technique is used. Quantitative and qualitative assays are done to check the level of HCV RNA in the serum for identifying the response to interferon treatment. [5] Many immunomodulatory therapies are given to improve the immune response of HCV infected patients. Other approaches include Therapeutic Vaccines, Modification to the interferon molecules, Protease inhibitors, Helicase inhibitors, and Molecular targeting etc. [19]

6. Future Aspects

Many steps and methods have been implemented to prevent and improve the HCV infection, which includes screening, testing, virus investigation. All these approaches have been very successful. However other strategies should also be introduced and taken into action in order to prevent the HCV infection, such as- risk reduction counselling, identification of HCV infection, rechecking of injections that had been used earlier, prevention of illegal drug injecting, improvement in identification of more specific reasons that figures out the activity and presence of pathogens in their hosts. [5], the interferon monotherapy, and drugs targeting either the host or virus, inhibits the viral replication which in turn increases the viral depletion rate. [6] Interferon Alfa was found to be effective inhibitor for Hepatitis C virus and its replication, for patients with liver transplantation, and also in therapeutic regulation. Ribavirin acts synergistically with interferon Alfa, and plays an important role in therapeutic regulation in the treatment of HCV infection. [26] . Hence there is a more challenge of innovation & sustainable development in this area of drug discovery against hepatitis-C in near future.

References

- 1.Doris B. Strader,1 Teresa Wright,2,3 David L. Thomas,4 and Leonard B. Serf5,6, Diagnosis, Management, and Treatment of Hepatitis C, DOI 10.1002/hep.20119
- 2.Markus Becklund,Kirsten Meyer,Michael von zielonka, and dieter eichenlaub, Treatment of Hepatitis C Infection in Injection Drug Users, doi:10.1053/jhep.2001.25882
- 3.Yao-Chun Hsu M.D., Chun-YingWu M.D., PhD., Jaw-Town Lin M.D., PhD., Hepatitis C Virus Infection, Antiviral Therapy, and Risk of Hepatocellular Carcinoma, SemenUncoil, <http://dx.doi.org/10.1053/j.seminoncol.2014.12.023>
- 4.Alison j. Rodger,1 Damien jolley ,2 Sandra c. Thompson,1 Anna lanigan,1 and nick crofts1, The Impact of Diagnosis of Hepatitis C Virus on Quality of Life
- 5.Miriam J. Alter, Prevention of Spread of Hepatitis C, doi:10.1053/jhep.2002.36389

6. Michael Charlton, Pre-emptive Treatment of Recurrent Hepatitis C Infection, doi:10.1053/jlts.2002.35859
7. Khayriyyah Mod Hanafiah,1 Justina Groeger,2 Abraham D. Flaxman,3 and Steven T. Wiersma4, Global Epidemiology of Hepatitis C Virus Infection: New Estimates of Age-Specific Antibody to HCV Seroprevalence, (HEPATOLOGY 2013;57:1333-1342)
8. Anna s. F. Lock and Naresh t. Gunaratnam, Diagnosis of Hepatitis C, (Hepatology 1997;26(Supply 1):48S-56S.)
9. Maxine M. Denniston,1 R. Monika Klevens,1 Geraldine M. McQuillan,2 and Ruth B. Jiles1, Awareness of Infection, Knowledge of Hepatitis C, and Medical Follow-Up Among Individuals Testing Positive for Hepatitis C: National Health and Nutrition Examination Survey 2001-2008, DOI 10.1002/hep.25556
10. Dima Dandachi,1,2 Manal Hassan,3 Ahmed Kaseb,4 Georgios Angelidakis,2 Harrys A Torres2,4, Hepatitis C virus-associated hepatocellular carcinoma as a second primary malignancy: exposing an overlooked presentation of liver cancer, Journal of Hepatocellular Carcinoma 2018;5 81–86.
11. Raymond T. Chung, M.D., and Thomas F. Baumert, M.D., Curing Chronic Hepatitis C — The Arc of a Medical Triumph, DOI: 10.1056/NEJMp1400986.
12. Jason Grebely,1 Gail V. Matthews,1 Andrew R. Lloyd,2 and Gregory J. Dore1, Elimination of Hepatitis C Virus Infection Among People Who Inject Drugs Through Treatment as Prevention: Feasibility and Future Requirements, DOI:10.1093/cad/cit3.
13. Stefan Zeuzem, M.D., Pietro Andreone, M.D., Stanislaus Pol, M.D., Eric Lawitz, M.D., Moises Diego, M.D., Stuart Roberts, M.D., Roberto Focaccia, M.D., Zobair Younossi, M.D., Graham R. Foster, F.C.R.P., Andrzej Horban, M.D., Peter Ferenci, M.D., Frederik Nivens, M.D., Beat Müllhaupt, M.D., Paul Pockros, M.D., Ruben Terg, M.D., Daniel Shovel, M.D., Bart van Hoek, M.D., Ola Weiland, M.D., Rolf Van Heeswijk, Pharm.D., Sandra De Meyer, Ph.D., Don Luo, Ph.D., Griet Boogaerts, M.Sc., Ramon Polo, Pharm.D., Gaston Piccolo, Ph.D., and Maria Beaumont, M.D., for the REALIZE Study Team*, Telaprevir for Retreatment of HCV Infection, N Engl J Med 2011;364:2417-28.
14. George ostapowicz,1 Katrina j. R. Watson,1 Stephen a. Locarnini,2 and Paul v. D esmond1, Role of Alcohol in the Progression of Liver Disease Caused By Hepatitis C Virus Infection, (HEPATOLOGY 1998;27:1730-1735.)
15. Stephany Joy Y. Macalino1, Vijay Kumar Gosul ,Sunny Hong1, Sun Choi1, Role of computer-aided drug design in modern drug discovery, Arch. Pharm. Res. DOI 10.1007/s12272-015-0640-5
16. Emma Day1, Margaret Hellard2, Carla Treloar3, Julie Bruneau4, Natasha K Martin5, Anne Øvrehus6, Olav Dalgard7, Andrew Lloyd8, John Dillon9, Matt Hickman10, Jude Byrne11, Alain Litwin12, Mojica Maticic13, Philip Bruggmann14, Harvard Midgard15, Brianna Norton12, Stacey Trooskin16, Jeffrey V Lazarus17*, and Jason Grebely8*, Hepatitis C elimination among people who inject drugs: Challenges and recommendations for action within a health systems framework, doi: 10.1111/liv.13949
17. Camps JI, Córdoba J, Esteban JI, Pathophysiology of hepatitis C virus infection, 1995 Oct;43(8):691-702.
18. Erzsébet SZABÓ, Gabor LOTZ, Casillas parka, Andres Kiss, Susa staff, Viral Hepatitis: New Data on Hepatitis C Infection, (Pathology Oncology Research Vol 9, No 4, 21 5–221)
19. M Bilodeau, D Lamarre. New treatment strategies against hepatitis C viral infection. Can J gastroenterology 2006;20(11):735-739.
20. Jennifer camwood, have: new opportunities, high cost, biotechnology healthcare · fall 2011
21. Viral hepatitis C testing by V Thorold and H Smith
22. Sylvie Raton, *, Monica Golumbeanub, Amelia Telenti c, Angela Ciuffia, exploring viral infection using single-cell sequencing, Virus Research 239 (2017) 55–68
23. Muhajir Mohamed, Ruchira Fernando, Diagnostic and Therapeutic Quandaries in a Patient with Primary Hepatic

Lymphoma and Concurrent Hepatitis C Infection, Indian J Hematic Blood Transfuse (Sept 2014) 30(Supple 1):S394–S397 DOI 10.1007/s12288-014-0431-z

24. Kenneth E. Sherman, M.D., Ph.D., Steven L. Flams, M.D., Nezam H. Afdhal, M.D., David R. Nelson, M.D., Mark S. Sulkowski, M.D., Gregory T. Everson, M.D., Michael W. Fried, M.D., Michael Adler, M.D., Ph.D., Hendrik W. Reskin, M.D., Ph.D., Marie Martin, Ph.D., Abdul J. Sakho, Ph.D., Nathalie Adda, M.D., Robert S. Kauffman, M.D., Ph.D., Shelley George, M.D., Christopher I. Wright, M.D., Ph.D., and Fred Poordad, M.D., Response-Guided Telaprevir Combination Treatment for Hepatitis C Virus Infection, N Engl J Med 2011;365:1014-24.

25. Prasanthi Polamreddy^{1,2}, Vinita Vishwakarma¹, Puneet Saxena², Identification of potential anti-hepatitis C virus agents targeting non-structural protein 5B using computational techniques, DOI: 10.1002/jcb.27071

26. T. Jake Liang, M.D., and Marc G. Ghany, M.D., M.H.Sc., Current and Future Therapies for Hepatitis C Virus Infection, N Engl J Med 2013;368:1907-17. DOI: 10.1056/NEJMra1213651.

