Medical Science Journal for Advance Research

Vol. 6, No.1, March 2025
e-ISSN: 2774-4892

Hepatitis C Virus (HCV) Infection, the Importance of Genotyping

Iman Jabbar Kadhim[1], Suaad Muhammed H. Rasheed[2], Wijdan Rajh Hamza Al-Kraity[3], and Falah Abdulhasan Deli[4]

[1,2,3]*Faculty of Medicine, University of Kufa, Iraq.*
[4]*Faculty of Medicine, University of Warith, Iraq.*
E-Mail: iman.alghizzi@uokufa.edu.iq, wijdanr.alkraity@uokufa.edu.iq

ABSTRACT

Background: *Hepatitis C virus (HCV) is an enveloped, single stranded positive-sense RNA virus discovered in the late eighties, circulating HCV antibody (anti-HCV) aided in diagnosis and screening of blood products minimizing post blood transfusion spread to a large extent, it is still highly prevalent in underdeveloped areas and it contribute largely to chronic liver diseases and hepatocellular carcinoma, One of the important features of HCV is its prominent genetic variability where new genetic polymorphism are emerging frequently and this has a great impact on treatment deciissions including the emergence of drug resistant strains among difeerent genotypes specially genotype 3, accordingly the Direct-Acting Antivirals (DAAs) including NS3/4A protease inhibitors, NS5A inhibitors and NS5B polymerase inhibitors are used in combination for patients initially treated and for those who have regimen failure. Unfortunately, still the studies of polymorphism and drug susceptibilities in Iraq are scarce and deficient.*

Keywords: Hepatitis C Virus, HCV, Infection, Genotyping.

Article Information
Received: January 3, 2025; Revised: February 18, 2025; Online: March, 2025

INTRODUCTION

Hepatitis C virus (HCV), belonged to family Flaviviridae, is an enveloped, single stranded positive-sense RNA virus with a genome of 9600 nucleotides in length, and 3000 amino acids are encoded in a single polyprotein cleaved into four proteins forming the skeleton (Core, Envelope 1 and 2, and p7) and six accessory proteins termed NS2–NS5B. The genome of hepatitis C virus (HCV) previously termed a non-A, non-B hepatitis virus was discovered in the late eighties where it was responsible for the dilemma of post transfusion hepatitis[(1,2)] and by applying recombinant technology on yeast, circulating HCV antibody (anti-HCVI) was developed aiding in diagnosis and screening of blood products[(3)], consequently the transmission through blood product was markedly reduced, and despite the fact that it is rarely transmitted vertically or through sexual practice like hepatitis B, it is still representing an important global medical problem where more than 60 million patients had persistent hypertransaminasemia and more than half of patients with acute HCV infection will develop chronic disease, more over even those with normal transaminase levels after recovery from acute phase, chronic hepatitis and liver cirrhosis can develop, in 2012 HCV represent the main cause of infection related mortalities surpassing all other infections combined and this is more obvious in elderly patients as HCV progression is very slow and insidious, the difference in susceptibility for development of chronic sequalae are related to viral and host factors[(4)]. HCV accounts for quarter of patients with liver cirrhosis and hepatocellular carcinoma [(5-9)].

https://doi.org/10.46966/msjar.v6i1.246

Published by: READ INSTITUTE

Approximately 4 million people are infected annualy through out the world, the prevalence is very low in USA (<1%) compared to 5% in certain parts of Africa and 2% in Egypt and Syria [7].

Genotyping of HCV

One of the important features of HCV is its prominent genetic variability caused by high instability of viral RNA polymerase and immune stress of the infected host. HCV is categorized into different genotypes termed from 1-7 and a novel genotype 8 found in panjab in india [10,11], genotypes are further divided into subtypes with divergence of a sequencing exceeding >15% with more than 85 subtypes termed (a, b, c…..) [12-13]

The importance of genotyping

Understanding the genotyping is critical for many

1. Epidemiological

Genotypes assessment give an idea about the epidemiology of HCV as genotypes occurs in different distribution in various geographic regions, and better knowledge of the dominant genotypes in any area can help the local health officials understand the impact of disease in their community and planning to treatment options and predicting drug resistance pattern, globally HCV genotype 1 is the most prevalent (more than 4%) , the subtypes 1a and 1b are prevalent mainly in North America, Europe, and Australia, while in Japan, more than 70% of patients have subtype 1b infection. Seconly in prevalence is Genotype 3 where it constitute a little less than third of people with HCV found mainly in South Asia, specially in people sharing needles of drug abuse.

2. Treatment Decisions

Drug therapy for HCV had a great change during the first two decades of the 21st century, the high occurrence of treatment failure with IFN based therapy (IFN-α alone or in combination with Ribavirin) was largely over countered with the introduction of Direct Acting Antivirals(DAA). The goal of treatment of patients with HCV is to reduce the occurrence of chronic inflammation and consequently the development of end stage liver disease and hepatocellular carcinoma and this is achieved by reaching sustained virologic response (SVR), the treatment is recommended in any patient with HCV whether acute or chronic except for those with short life expectancy. Patients in whom SVR is achieved have HCV antibodies with undetectable HCV RNA in serum, liver tissue, or mononuclear cells, and have noticeable improvement in liver histopathology[14] The Direct-Acting Antivirals (DAAs) includes NS3/4A protease inhibitors, NS5A inhibitors and NS5B polymerase inhibitors, use combinations of DAAs to enhance efficacy and minimize the risk of resistance[11].

A huge work had been achieved for discovering and developing novel direct-acting antivirals (DAAs), HCV has a high genetic diversity property to change their antigenic charecterestics according to hosts challenges and consequently the rapid aquasition of drug resistance. High efficacy was achieved by NS5B HCV inhibitor sofosbuvir (SOF) combined with other agents against most genotypes [15-17]. Moreover combining NS5A inhibitor velpatasvir (VEL) with SOF demonstrated high rates of SVR in patients with and without treatment failure, including those with compensated cirrhosis [14]. Should DAA regimen Fails, a fixed-dose combination of SOF/VEL and the protease inhibitor voxilaprevir (VOX) provides high rates of SVR [18]. Genotyping is critical in deciding the best treatment option and leads to more personalized treatment plans, improving SVR, and here are some examples

Genotype 1: This is the highly prevalent genotype and is usually responding to direct-acting antivirals (DAAs) like sofosbuvir and ledipasvir, adding Ribavirin to DAAs will not change the SVR in patients receiving DAAs as was documented in several meta-analysis studies [19-21]

Genotype 3: This genotype has the more frequent drug resistance pattern and accordingly requires combination therapy for prolonged time, it is more prevalent in Asia and in injectable drug users, furthermore it had shown to disturb glucose and lipid metabolism, and the progression of liver disease is more rapid with increasing chance for hepatocellular carcinoma (HCC). The enhanced response to protease inhibitors by genotype 1 is largely halted in genotype 3 [22-23, 26]

3. Resistance Patterns

Certain genotypes may be associated with specific resistance patterns to antiviral drugs and this is especially true for genotype 3, and in addition to the higher prevalence of drug resistance in low and medium income areas, the poor resources for recognition of resistance pattern is complicating the problem. Recognizing resistance patterns can help clinicians anticipate treatment challenges and adjust strategies accordingly and this needs a hard work by local health authorities[24-25,27].

CONCLUSIONS

Effective treatment of drug-resistant HCV requires a thorough understanding of the genotyping of the virus supplemented with careful understanding and follow-up of treatment response to ensure favorable outcomes and this is supplemented with proper adherence for therapy with appropriate drug selection to avoid resistance development.

RECOMMENDATIONS

Unfortunately, the studies in Iraq for this issue are still scarce and limited, and there is a great need for the assessment of proper treatment regimens based on serological studies of genotyping and following the most agreeable guidelines for therapy

REFERENCES

1. Choo Q-L, Kuo G, Weiner AJ, Overby LR. Bradley DW, Houghton M. Isolation of a cDNA derived from a blood-borne non-A. non-I3 viral hepatitis genome. Science 1989;244:359-362.

2. Kuo G, Choo Q-L, Alter HJ, Gitnick GI, Redeker AG, Purcell RH. Miyamura T, et al. An assay for circulating antibodies to a major etiologic virus of human non-A. non-B hepatitis. Science 1989: 244:362-364

3. Alter HJ, Purcell RH, Shih *JW*. Melpolder JC. Houghton M, ChooQ-L, Kuo G. Detection of antibody to hepatitis C virus in prospectively followed transfusion recipients with acute andchronic non-A, non-B hepatitis. New Eng J Med 1989:321:1494-1500

4. Reddy KR, Pol S, Thuluvath PJ. Long-term follow-up of clinical trial patients treated for chronic HCV infection with daclatasvir-based regimens. Liver Int. 2018;38(5):821-833.

5. American Association for Study of Liver Diseases (AASLD), Infectious Diseases Society of America (IDSA). Recommendations for testing, managing, and treating hepatitis C [Updated August 2020]. Available from: www.hcvguidelines.org.

6. Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, et al. Global distribution and prevalence of

hepatitis C virus genotypes. Hepatology. 2015;61(1):77–87

7. Global burden of disease (GBD) for hepatitis C. J Clin Pharmacol. 2004;44:20–29

8. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol. 2006;45:529–538.

9. European Centre for Disease Prevention and Control. Introduction to the Annual Epidemiological Report. In:ECDC. Annual epidemiological report for 2017. Stockholm: ECDC; 2017

10. Smith DB, Bukh J, Kuiken C, et al. Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: updated criteria and genotype assignment web resource. Hepatology 2014; 59:318–27

11. Schreiber J, McNally J, Chodavarapu K, et al. Treatment of a patient with genotype 7 hepatitis C virus infection with sofosbuvir and velpatasvir. Hepatology 2016; 64:983–5.

12. Cuypers L, Li G, Libin P, Piampongsant S, Vandamme A-M and Theys K. Genetic Diversity and Selective Pressure in Hepatitis C Virus Genotypes 1–6: Significance for Direct-Acting Antiviral Treatment and Drug Resistance. Viruses. 2015; 7: 5018–5039

13. Ramia S. and Eid-Fares J. Distribution of hepatitis C virus genotypes in the Middle East. International Journal of Infectious Diseases. 2006; 10:272-277.

14. Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. Ann Intern Med. 2013;158(5 Pt 1):329-337.

15. K Rajender Reddy , Marc Bourlière , Mark Sulkowski et al Ledipasvir and sofosbuvir in patients with genotype 1 hepatitis C virus infection and compensated cirrhosis: An integrated safety and efficacy analysis. Hepatology. 2015 Jul;62(1):79-86.

16. Tam E, Luetkemeyer AF, Mantry PS et al. Ledipasvir/sofosbuvir for treatment of hepatitis C virus in sofosbuvir-experienced, NS5A treatment-naïve patients: Findings from two randomized trials.Liver Int. 2018 Jun;38(6):1010-1021.

17. Charlotte Hedskog, Bandita Parhy, Silvia Chang et al Identification of 19 Novel Hepatitis C Virus Subtypes—Further Expanding HCV Classification Open Forum Infect Dis. 2019 Feb 22;6(3)

18. Lam AM, Espiritu C, Bansal S, et al. Genotype and subtype profiling of PSI-7977 as a nucleotide inhibitor of hepatitis C virus. Antimicrob Agents Chemother 2012; 56:3359–68

19. Zeuzem S, Dusheiko GM, Salupere R, et al. ; VALENCE Investigators Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med 2014; 370:1993–2001

20. Bourlière M, Gordon SC, Flamm SL, et al. ; POLARIS-1 and POLARIS-4 Investigators Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection. N Engl J Med 2017; 376:2134–46.

21. 20- Thokala P, Simpson EL, Tappenden P. Ledipasvir-Sofosbuvir for Treating Chronic Hepatitis C: A NICE Single Technology Appraisal-An Evidence Review Group Perspective. Pharmacoeconomics. 2016 Aug;34(8):741-50.

22. J Ampuero, M Romero-Gómez, K R Reddy HCV genotype 3 – the new treatment challenge Aliment Pharmacol Ther 2014 Apr;39(7):686-98.

23. World Health Organization (WHO) *Global hepatitis report 2024: action for access in low- and middle-income countries* Geneva, Switzerland World Health Organization (WHO), 2024

24. Seth Inzaule, Philippa Easterbrook, Ashley Latona et al Prevalence of Drug Resistance Associated Substitutions in Persons With Chronic Hepatitis C Infection and Virological Failure Following Initial or Re-treatment With Pan-genotypic Direct-Acting Antivirals: A Systematic Review and Meta-analysis *Clinical Infectious Diseases*, Volume 79, Issue 6, 15 December 2024, Pages 1437–1446

25. Feld JJ, Jacobson IM, Hézode C, et al.; ASTRAL-1 Investigators Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. N Engl J Med 2015; 373:2599–607

26. Noor A. Khdeir, Hayder A. Maklef Al-Hmudi, Safauldeen A. Alhajim. Genotyping of Hepatitis C Virus (HCV) in Patients of Basra Province/Iraq International Journal of Innovative Research in Science, Engineering and Technology Vol. 5, Issue 6, June 2016.

27. Dlshad A Hassan , Sazan Q Maulud , Rastee H Saeed et al Seroprevalence and Genotypic Distribution Patterns of Hepatitis C Virus among Infected Patients from Erbil Province: Kurdistan/Iraq Diyalad J med, Volume 14, Issue 1, 2018, 84-93.

