Original Article

Genomic divergence of Hepatitis C virus towards common prescribed interferon regimens on sustained virologic response (SVR)

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ABSTRACT

Hepatitis C is one of the dangerous diseases which if left untreated can cause the loss of life. The study's main to detect HCV RNA in Hepatitis C patients using a real-time polymerase chain reaction to determine the genotype distribution pattern, and role of its genomic divergence toward commonly prescribed interferon regimens. A cross-sectional study with 980 patients was conducted in a tertiary care hospital were chosen and their blood samples were collected which was screened. Real-time PCR was used to quantify HCV-RNA in seropositive Hepatitis C patients, and genotyping for HCV was performed in HCV-RNA positive samples at Agha Khan laboratories, and in addition to this, the well-structured questionnaire was also distributed. From the total sample size (65.22) male patients were taken and 313(34.77%) were female patients. Generally, Peg-interferon treatment was used by 10% of clinicians with all HCV genotypes. 85.56% of Physicians prescribed conventional interferon, and to treat HCV-positive patients, 14.44 % were recommended peg-interferon in combined application with ribavirin. Peg-interferon was predominantly used in HCV-positive patients with genotypes 1a and 2a (55% and 37% respectively). Clinicians also used Peg-Interferon in certain cases (10%) among patients with genotype 3a. Genotype-3a is the predominant allele in the Bannu district, and Because resistant types necessarily involve the use of peg-interferon therapy, pre-treatment genotyping is critical in the selection of treatment schedule.

Keywords: Hepatitis C, Frequency, Cirrhosis, Genotypes, Peg-interferon therapy

Introduction

The Hepatitis C virus (HCV) is a significant issue of public health that impacts 170 million people globally. It represents the most prevalent cause of chronic hepatitis, cirrhosis, and liver cancer worldwide, as well as the principal reason for liver transplants [1, 2], and some research revealed that HCV-related mortality (death from liver failure or hepatocellular carcinoma) will keep going up throughout the next couple of decades [3].

Hepatitis C virus (HCV) infection is getting more widespread all over the world. Pakistan (4.8 percent), Egypt (22 percent), and China (3.2 percent) have the highest rates of chronic Hepatitis C infection [4, 5]. In accordance with the WHO, approximately estimated of morbidity rate as 130-170 million people are chronically infected with the Hepatitis C virus, and over 350,000 is mortility rate from Hepatitis C-related liver diseases [6]. Acute hepatitis C occurs within the initial 6 months of infection with the hepatitis C virus. It is usually mild and nonspecific, but it frequently leads to a specific diagnosis of hepatitis C. A lack of appetite, lethargy, abdominal discomfort, itching, jaundice, and flu-like symptoms are all symptoms of acute hepatitis C infection. Acute HCV infection is uncommon and, in estimated 80% of cases, is linked to long-term infection [7]. Initial

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symptoms can occur 7 to 8 weeks after HCV exposure, however, the vast majority of people have no and perhaps only mild symptoms, and severe liver failure due to acute HCV infection is extremely rare. Even though clinical symptoms occur in less than 25% of infected individuals [8]. Whereas most infections are becoming chronic, as long as cirrhosis and hepatocellular carcinoma aren't prevalent, chronic infection is either symptomless or has only faint vague and general symptoms such as fatigue, chronic hepatitis C is clinically asymptomatic (no jaundice) and is frequently acquired accidentally [9, 10].

The global prevalence of Hepatitis is approximately 1.6 percent, with a viraemic rate of about 1.1 percent, affecting about 80 million global populace, and more than 71 million individuals globally have chronic Hepatitis C infection, which can lead to liver cirrhosis. There is currently no clear HCV vaccine available right now an estimated 399000 people die each year from hepatitis C, predominantly cirrhosis and HCC [11].

The phylogenetic analysis of HCV isolates from various parts of the world demonstrated six major hepatitis C virus (HCV) genotypes, known as types1-6, as well as various subtypes [12], and a newly discovered seventh type (Innogenetic). Variants isolate obtained predominantly in Southeast Asia were discovered to differ among types and subtypes [13, 14]. They were integrated into their nearest phylogenetic type (all type 6, except one type 3 strain). The allocation of HCV genotypes represents hepatitis C transmission dynamics and therefore is firmly related to spesific modes of transmission [15]. Genotype is an important predictors of response to antiviral combination therapy with interferon (IFN)-a and ribavirin. Genotype 1 has attained the highest prevalence worldwide and has got 46% distribution worldwide followed by Genotype 3 with 22%. It has been observed that 85% of the patients develop chronic hepatitis who once got an acute infection of hepatitis [16]. Pakistan is 2nd most affected country with a prevalence of hepatitis, no study before this has been published to evaluate this issue hence this study will be the pioneer to determine the efficacy of anti-HCV based on genotypes. Hence there was a dire need to address such a topic and scientific work was needed to highlight this disease, as a result, Thus the present study aims to provide a detailed explanation of the role of HCV genotypes in effective HCV infection treatment.

Materials and Methods

An analytical cross-sectional study was carried out among a total of nine hundred eighty (980) Hepatitis-C positive patients were included from different clinics "In Khyber Pakhtunkhwa during the study period from February to August 2021. All the participants suffering from Hepatitis C were included in this study their ages ranged from 18 to 70 years. Those patients who had other diseases along with Hepatitis C, mentally unsound patients, and patients admitted to the ICU were excluded. Those who did not show interest were excluded from the study too.

All hepatitis C patients had a post-treatment PCR. Eighty patients were ruled out since they did not meet the inclusion criteria. As a result, clinical outcomes in hepatitis C were assessed and compared using various models of regular interferon plus ribavirin and Peg-interferon plus ribavirin depending on post-treatment PCR. Seventy physicians were asked to complete questionnaire forms, and their responses were compiled. First of all, a set of participants who received treatment was gathered from different hospital clinics and laboratories of selected districts of "Khyber Pakhtunkhwa". By figuring the patient data, the males were separated from the females. Those patients who dropped out or whose treatment was insufficient were removed, and a list of those who accomplished the six-month Hepatitis-C therapies was created. Hence treatment compliance was calculated focused on this records. and finally, the blood samples were sent to Agha Khan Laboratory to screen out the type of genotypes. The questionnaire was developed by the principal author in consultation with the clinical Pharmacist and physician working in the Gastro ward of the Hospital. In addition to this, the Hospital was selected based on the area where the maximum prevalence of hepatitis was noticed and that was the Bannu division where the number of Hepatitis patients was reported to be 1 million.

Ethical approval

This study was approved and sought from the government hospital of Banuu where the study was carried out, and each participant supplied informed consent. P values equal to or less than 0.05 were regarded as statistically significant when using the Statistical Package for Social Sciences (SPSS) software version 26.

Results and Discussion

Table 1 illustrates the baseline demographic data of study participants, where the majority of participants (65.22%) were male, and 43.36% were in the age group 41-60 years old. Treatment regimen. 85.56% of Physicians prescribed conventional interferon, and among HCV-positive participants, 14.44 percent were given a prescription peg-interferon in combined application with ribavirin (Prescribing information of uniferron) for treatment. **Table 2** demonstrated the allocation and way to respond to proformas of specialists and general practitioners enrolled in the study, where the overall rate of responses is70%, which is regarded as a healthy and corporative response from healthcare professionals recruited in the study.

Table 1. Baseline demographic data of study participants

	Frequency n=980	Percentage %
Gender		
Male	587	65.22%
Female	313	34.77%
Age group		
20-40 Years old	367	37.44
41-60 Years old	425	43.36%
61-80 Years old	188	19.18%
Prescribed treatment		
Conventional interferon + Ribavirin	839	85.56%

Peg-interferon + Ribavirin	141	14.44%
Total	980	100%

Table 2. Over all Distribution of proformas to the physicians and their Response

Total No. of proformas	FCPS	GPs	Response		%age		Over all % response
			FCPS	GPs	FCPS	GPs	
100	64	36	46	24	71.9	66.6	70

*GPs: General Practitioners, FCPs: Fellowship of collage of physicians and Sergons

Table 3 demonstrated that pre-treatment genotyping is critical in the choice of treatment schedules since resistant types necessitate the administration of peg-interferon therapy, and thus there is a further need for Physicians' permission to patients that pre-treatment genotyping is essential, regardless of the expense of the genotyping test.

Table 3. Frequency and prevalence of genotypes

	Genotype 1	Genotype 2	Genotype 3	Genotype 4	Genotype 5	Genotype 6
1.	12.73%	3.11%	65.52%	18.64%	N/A	N/A
2.	0	8.27%	90.55%	1.18%	0	0

According to **Figure 1**, peg-interferon was primarily used in HCV-positive patients with genotypes 1a and 2a (55 percent and37 percent respectively). Although in 10% of genotype 3a cases, clinicians used Peg-Interferon. In general, clinicians had to use peg-interferon therapy for all genotypes of HCV-positive patients; nevertheless, the use of peg-interferon is limited to enabling patients because it is expensive.

Epclusa is a single pill that contains a fixed-dose combination of two HCV-fighting drugs (sofosbuvir and velpatasvir). It is prescribed for individuals with all hepatitis C genotypes (1–6). Epclusa is considered once daily for 12 weeks, with or without food. Individuals who have severe (decompensated) cirrhosis would need an extra drug called Ribavirin twice daily, based on the data in **Table 4**.

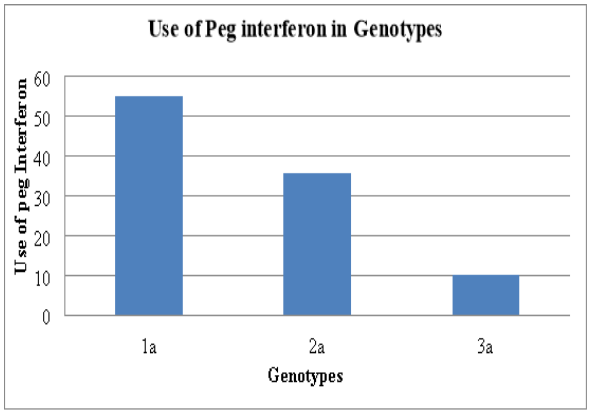

Figure 1. Use of interferon in genotypes

Table 4. Treatment based on different types of genotypes

Genotype	Cirrhosis	Type of Therapy	Duration of Therapy	Sustained Virologic Response
1,2,4,5,6	No cirrhosis	Epclusa	12 weeks	98%
3	No cirrhosis	Epclusa	12 weeks	94%
1,2,4,5,6	Decompensated cirrhosis	Epclusa+ Ribavirin	12 weeks	93%
3	Decompensated cirrhosis	Epclusa+ Ribavirin	12 weeks	82%

HCV emerged as the first virus discovered using biomolecule cloning rather than biologic or biophysical mechanisms. This was accomplished by extracting, copying, and cloning all of the nucleotides from the blood of a chimp infected with non-A, non-B hepatitis using contaminated factor XIII concentrate. The HCV genome is a proactive, single-stranded RNA genetic code that is approximately 10 kb long. It is strikingly similar to Pestivirus and Flavivirus representatives. Diverse HCV isolates all over world have significant genomic differences throughout the viral genome. HCV has been categorized into various cultivars depending on such genomic disparities. Several of the discrepancies in clinical outcomes and treatment response, as well as disease prognosis demonstrated among HCV-infected individuals, are suggested to be related to HCV genetic heterogeneity [17]. Hence a current study was aimed to detect HCV RNA in Hepatitis C patients using a real-time polymerase chain reaction to determine the genotype distribution pattern, and role of its genomic divergence toward commonly prescribed interferon regimens

Hepatitis C genotype is classified into six distinct genotype classes, each with multiple subtypes. Chronic Hepatitis C genotypes include:

1. 1a and 1b Genotypes
2. 2a, 2b, 2c, and 2d genotypes
3. Genotypes 3a-3b, 3c-3d, 3e-3f

4a, 4b, 4c, 4d, 4e, 4f, 4g, 4h, 4i, and 4j

5. 5a Genotype

6a (Genotype)

HCV genotypes diverge in three main characteristics, emphasizing the significance of genetic variability among HCV genotypes: Firstly; The incidence of particular HCV genotypes is mainly related to geographical ranges; for example, HCV genotype 1 is common in North of America and Japan, while genotype 3 is common on the Indian subcontinent, genotype 4 is common in Africa and the Middle East, genotype 5 can be found in South Africa, and genotype 6 in Southeast Asia [18]; Secondly; the HCV pathogenicity flucctuate by genotype; as, HCV genotype 1 is pathogenic in North America. HCV genotype 3 is related to a higher degree of liver steatosis [19] and genotype 1 disease is associated with a higher likelihood of developing HCC [20], and thirdly an IFN-based therapeutic interventions response rates differ considerably between the different HCV genotypes [21].

The most common type of Hepatitis C genotype in the United States is genotype 1, which is extremely challenging to treat. The genotype of Hepatitis C is critical for healthcare professionals in making pharmacotherapy guidelines. Patients with genotypes 2 and 3 of hepatitis C are nearly three times more likely than patients with genotype 1 to give a response to antiviral therapy with alpha interferon or the combination of alpha interferon and ribavirin. Furthermore, during using combination therapy for hepatitis C, the suggested treatment period is genotype dependent. As a result, screening for the Hepatitis C genotype is frequently diagnostically advantageous. When ascertained, the genotype would never alter, and it is not necessary to check again since genetic variants do not modify during Interferon therapy. In the case of genotype, our findings are in accordance with those reported by Idrees *et al.* 2009 who discovered that chronically infected infection was the most common threat in Pakistan, accounting for 67.12 percent of registered HCC (hepatocellular carcinoma) subjects, and genotype 3a in 41.16 percent, 3b in 16.16 percent, 1a in 8.61 percent, and 1b in 2.49 percent of HCC tissue samples [22]. The sustained virological response (SVR) of Antiviral therapy obviously varies based on the genotype, dosages, and Interferon type used to treat that specific genotype of HCV. HCV genotype 1,2,4,5, and genotype 6 infections among patients without liver cirrhosis showed an excellent response rate of the treatment period to genotypes 3 (12wk); while HCV genotypes 1,2,3 and 4 with decompensated cirrhosis are superior responsive to PEG-IFN/RBV treatment, with a sustained virological response (SVR) rate hovering around 93% compared with genotype 3 virological response (SVR) rate was 84%. Such findings were in agreement with different studies that conclude that HCV genotypes 1 and 4 require a prolonged treatment period of more than (48 weeks) than genotypes 2 and 3 (24 weeks); HCV genotypes 1 and 4 are much less sensitive to PEG-IFN/RBV intervention, with a sustained virological response (SVR) rate with about 50% [23, 24].

The variations observed in SVR rates between HCV genotypes suggest that the variability of viral genomes may have an important impact in therapeutic potential. Nevertheless, it is still ambiguous which genetic element(s) within the Genomic sequence is willing to take responsibility for the disparity in treatment response rates among HCV genotypes. A sequence of comprehensive molecular phylogenetics has revealed a strong significant relationship between the developmental age of HCV genotypes and response rates to IFN-based therapeutic interventions [25].

The current results showed agreement with what was stated in the previously published literature and that gene A is the most common in the Indian subcontinent. Interestingly our findings revealed that slow responders (Decompensated cirrhosis) have a relatively high relapse rate in genotype 3 infection with the standard therapy duration of 12 weeks, especially in comparison to those whose Hepatitis C virus eliminate earlier in the treatment approach (12 weeks). This finding is in contrast with a study conducted by Ferenci *et al*. [26] who noted the same conclusion but in genotype 1, and high rates of relapse in slow responding patients may imply that treatments were inadequate and lengthy; consequently, it has been postulated that prolonging medication in these patient populations may optimize rates of SVR. The conflict in genotypes is attributed to the difference in ethnic groups as genotype 3 is more prevalent in Pakistan.

Certainly study done by Pearlman *et al*. [27] explore that SVR achieved for genotype 1a was 36 percent (103/285) with traditional interferon (interferon alpha-2b) and ribavirin 1 to 1.2 mg for 12 months study (Pegasys prescribing information), while SVR was 84 percent (81/96) when peg-interferon (180g) plus ribavirin (800 mg) was administered in genotype 1a and 2a for 24 weeks. The dose of peg-interferon used in all of the previous cases was the same (prescribing information of Pegasys). All of these studies suggests that the SVR is affected by the duration of therapy, the dose of the chosen regimen, and the type of interferon. IFN is presently the cornerstone of HCV possible treatments. The gold standard for treating chronic hepatitis C infection of various HCV genotypes is combination therapy with pegylated-IFN and ribavirin (PEG-IFN/RBV). Furthermore, therapeutic continuation in critically ill and slow responders with genotype 3 may be a satisfactory approach for enhancing therapeutic efficacy in these treatment-refractory patients, based on both viral kinetics and our laboratory findings.

Conclusion

HCV genotyping perior treatment is much critical in treatment scheduling system selection because resistant types necessitate the use of peg-interferon therapy. Genotype-3a is more common in the Bannu district, and therapeutic continuation in critically ill and slow responders with genotype 3 may be a satisfactory approach for enhancing therapeutic efficacy.

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Conflict of interest: None

Financial support: None

Ethics statement: The study was conducted according to the guidelines manifested in the Declaration of Helsinki, and written informed consent was obtained from all enrolled participants. The study procedure was approved by the local government hospital of Banuu/Khyber Pakhtunkhwa province in Pakistan where the study was carried out.

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