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The role of hepatitis C virus genotyping in evaluating the efficacy of INF-based therapy used in treating hepatitis C infected patients in Libya

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Abstract

Background: Hepatitis C virus (HCV) therapy has been evolved over years and many parameters were used to evaluate such therapy particularly genotyping. In North Africa and Eastern Mediterranean the genotypes vary from most of world and rarely studies were conducted to assess the influence of such genotypes on the HCV therapy.

Aims: This study was designed to determine; the role of HCV genotyping in assessing the efficacy of interferon therapy and to analyze the rates of sustained virological response (SVR) in INF and PegIFN-based regimens according on HCV genotype infecting Libyan patients with chronic hepatitis C infection.

Methods: A total of 479 patients with chronic HCV registered at Tripoli Medical Centre were treated with 'INF alfa or PEG-INF- Pegylated INF alfa 2a in combination with ribavirin' for a five year period. These patients were registered and followed up from January 2007 to October 2012. The information were reviewed and data were collected from each patient regarding age, gender, ALT level, and viral load, viral genotype using qualitative PCR. The statistical analysis were carried using SPSS version 11.5.

Results: Of the patients studied 86 patients were treated with INF based regimen, only 54% of them had end treatment response (ETR) and 28% had SVR. Off 143 patients treated with peg-INF alfa 2a based therapy; 69% had ETR and 36% had SVR. The SVR of Peg-INF based regimen was higher than INF based regimen in all genotypes except for genotype 4. The relationship between SVR and gender was significant in patients who were given INF based therapy comparable to PEG INF based regimen, though the relationship between SVR and age, basal viral load and basal ALT were also reported in both regimens.

Conclusions: HCV genotyping has been found to play an important valuable role in determining the efficacy of Hepatitis C therapy. SVR vary according to the HCV genotype involved. HCV genotype 1 and 4 were found to be the prevalent resistant genotypes infecting Libyan patients. Such findings are particularly important in guiding the clinical therapy of patients infected with hepatitis C virus.

Keywords: Hepatitis C virus, interferon, Libyan patients, HCV genotypes

Introduction

Hepatitis C virus (HCV) has been considered to be one of the most ongoing causes of viral hepatitis. Deaths due this virus are expected to be tripled in next 20 years, particularly among developing countries [1]. This imposes a major personal and social burdens on infected individual further to a heavy economic hurdles on health and insurance sectors [2]. Hence then having proper valuable therapy, easily monitored will be priority for clinicians and researchers involved in the management of HCV infection.

Treatment of Hepatitis of C infection has been evolved over years and many regimens has been introduced [3,4]. The early used drug was interferon (INF) alpha; the addition of a polyethylene glycol (Peg) moiety to INF (termed, Peg-INF) has dramatically enhances its span life in blood and thus it reduces the needed dose [5,6]. This efficiency was significantly improved with the addition of guanosine analogue ribavirin (RBV). Combination therapy particularly (Peg-INF) with RBV has been considered to be effective therapies for chronic HCV [7,8]. Such therapy was not well tolerated with all patients. Hence then more effective and tolerable treatments were introduced among them, direct-acting antiviral (DAA) drugs such as telaprevir, and boceprevir, which were approved for clinical use recently [9,10]. These could be used in combination with pegylated interferon and ribavirin particularly in treatment-na¨ıve and problematic patients [11]. Despite the increasing advancement in such therapy and the ultimate increase in the clearance rate which reached up to 80% in different clinical trials, emergence of resistant viral variants has been reported [12]. Hence then, therapy of HC Infection should be effectively monitored and different parameters were introduced to assess its efficacy. Both host and viral factors were found to be associated with such treatment particularly with non-response to PEG-INF. Viral factors include viral load, genotype and quasi-species of

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HCV. Each patient should be anticipated to follow a specific criterion that might include, progress of disease, predisposing factors, symptomology and viral status [13,14].

Hepatitis C Genotyping plays an important role in the clinico-epidemiological manifestations of HC infection and the existence of six major types virus genotypes and about 100 subtypes, which, have been identified with distinct geographic distributions. Genotypes 1, 2 & 3 accounted for the majority of HCV infections worldwide [15]. Genotype-1, the most common genotype, it is dominant in USA, Europe and most Asia-Pacific [16]. Genotype-2 in Japan, South Korea and southern Taiwan [17,18]. Genotype-3 is prevalent on the Indian subcontinent and Australia. Genotype-4 is predominantly found in the Middle East and North Africa [2] though genotype -5 was limited to South Africa [19], and HCV-6-11 was found in South-East Asia [20]. Such variation starts to change due worldwide massive social surge and cultural diversity.

HCV genotype is the strongest baseline predictor of IFN response and the efficacy of HC therapy has been influenced by HCV genotypes and different genotypes showed different clinical responses to HCV therapy. Hence then, the use of HCV genotyping in assessing the therapy of Hepatitis C infection is becoming valuable important aspect [9,21]. Monitoring of HCV drug resistance before and during treatment is likely to provide important information for management of patients undergoing anti-HCV therapy. The objectives of this study were to evaluate the efficacy of IFN and peg-INF-based regimens and determine factors that influence the response and resistance of the regimens used and the role of HCV genotyping in predicting on monitoring the response of such therapy.

Patients and methods

Patients population

A total of 479 patients with hepatitis C virus were studied. The patients were recruited from the Department of Infectious Diseases at Tripoli Medical Centre, Tripoli. All were registered and followed up at Out Patient Department from January 2007 to October 2012. Three hundred and three patients were male and 176 patients were female. (Male; Female ratio 1.7:1). The age was ranged from16 to 84 years with an average age of 40 years at the entry of the study.

The data collected was designed to extract information from patients that may influence the outcome of viral therapy such as age, gender and year of diagnosis of HCV. The participation was voluntary in accordance of with the guidelines for observational and interventional studies of national ethical committees as the research was conducted according to Helsinki Declaration [22] and Libyan National committee for ethical approval number LETC/THCV-T77/2006.

Patient exclusion criterion

Each patient has to fulfil the specific criteria that include; no co infection with human immune-deficiency syndrome (AIDS) virus or with hepatitis B virus and HDV, and none of them had liver cirrhosis, or undergo haemodialysis; and no concomitant metabolic or autoimmune disorder or underlying systemic diseases.

Study design

This randomised clinical study was conducted at Tripoli Medical Centre as patients were randomly assigned. Antiviral therapy was administrated to 229 patients, 86 patients were given INF-alfa plus Ribavirin combination therapy and 143 were given pegylated interferon-alfa 2a plus Ribavirin combination therapy. The INF alfa dose were 3 million IU subcutaneously three times a week for 24 weeks for genotypes (2 and 3) and for 48 weeks for genotypes (1 and 4). The Peg INF-alfa 2a was given as fixed dose of 180 microgram once a week for 24 weeks for genotypes (2 and 3) and for 48 weeks for genotypes (1 and 4). Ribavirin was given as 800 mg daily dose, 200-mg capsules twice a day in combination with INF or Peg INF for 24 weeks for genotypes (2 and 3) but for genotypes (1 and 4) the full daily dose was adjusting according to body weight 1.000 mg daily dose for patients weighted 75kg or less and 1.200 daily dose if patients weighted more than 75 kg the dose was given twice a day in combination with INF or Peg-INF for 48 weeks. End treatment response (ETR) was defined as undetectable HCV RNA at the end of treatment which takes at least 12 weeks. Sustained virological response (SVR) was defined as undetectable HCV RNA at 24 weeks after completion of treatment.

Laboratory and Clinical Evaluation of HCV Infection Virological Studies

A serum specimen was collected from each patient and was tested positive for HCV antibody (Anti-HCV) using and 3rd generation commercial Enzyme Linked Immunosorbant Assays (ELISA) The INNO-LIA™ HCV Ab III update is 3rd generation line immunoassay which incorporates HCV antigens derived from the core region, the E2 hyper-variable region, the NS3 helicase region, the NS4A, and NS5A regions. The antigens were coated on a nylon strip with plastic backing as 6 discrete lines. Then, in each strip every four control lines were coated: strepavidin control, 3+Positive Control (anti-human Ig), 1+Positive Control (human IgG) and+cut-off line (human IgG). Incubated with test sample then purified alkaline phosphatase was added–labelled goat anti–human IgG and lastly we added conjugate [1].

Determination of HCV genotypes

The genotyping in this study was carried out by gene amplification using COBAS-Amblicor HCV test as early described [1], detected by reverse-transcribing HCV RNA into cDNA by PC, hybridizing amplified cDNA with an oligonucleotid probe that binds enzyme, and catalyzing conversion of substrate to a colored product that is recognized by COBAS AMBLICOR Analyzer (Roche, Diagnostic, Basal, Switzerland).

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Table 1. Base line clinical characteristics of patients enrolled for the study.

Clinical Characteristics	Number of Patients(%)
Patients population	
Total patients involved	479(100)
Male	303(63.3)
Female	176(36.8)
Age in years	16-86
Patients disposition	
Refused treatment	149(31.10)
Involved in the treatment	372(77.7)
Finished Treatment	229(47.8)
Discontinued treatment	143(29.9)
Virologica response	
Response to Inf based regimen	70(14.6)
Response to Peg Inf based regimen	149(30.9)
Monitoring viral response	
Alanine aminotransferase, IU/L HCV-RNA level	219(45.7)
< 200,000 IU/ml	130(27.1)
> 200,000 IU/ml	89(18.6)

Determination of viral load

HCV load was performed by COBAS^{R} TaqMan^{R} HCV Test, v2.0 which based on three major processes [1] manual specimen preparation to extract HCV RNA, [2] automated reverse transcription of the target RNA to generation complementary DNA, [3] PCR amplification of target cDNA using HCV specific complementary primers and simultaneous detection of cleaved dual fluorescent dye- labelled oligonucleotide probes. The Master Mix reagent contains primer pairs and probes specific for both HCV RNA and HCV Quantitation Standard RNA as previously published [1]. The detection of amplified using target specific and Quantitation Standard specific dual labelled oligonucliotide probes that permit independent identification of HCV amplicon and HCV Quantitation Standard amplicon, and also quantitation of HCV viral RNA is performed using the HCV Quantitation Standard. The test has limits of detection approximately 50 IU per ml, (Roche, Diagnostic, Basal, Switzerland). Biochemical parameters such as ALT (alanine aminotransferase) (GPT) and AST (aspartate aminotransferase) (GOT) were also analysed and evaluated for each patients.

Statistical analysis

Quantitative variables were expressed as mean ± standard deviation and were compared by Student's test (t-test). Differences in proportion of qualitative variables were tested with non–parametric tests (X2) Yates correlation. Fisher exact test and a p value < 0.05 were considered significant. A multivariate analysis was conducted using logistic regression in order to verify which variables statistically had an influence on HCV infection. such as gender (male vs. female), IV drug abuser (yes or no), blood transfusion (yes or no) surgical Intervention (yes or no), dental care (yes or no); Heterosexuality and homosexuality (yes or no). The calculation of 95% Confidence Interval (CI) to compare groups was determined and the data were analyzed using SPSS version 11.5 to evaluate the efficacy of therapy and its association with genotypes, gender, ALT, viral load, and also to assess the sustained virological response (SVR) in different genotype, and finally the different regimens of therapy efficacy were compared.

Results

Efficacy of HCV therapeutic regimens

Initially 479 patients with chronic HCV were recruited to be included in this study their clinical characteristics were shown in **Table 1**. Off 107 (22.3%) patients of them were withdrawn from the study, as they refused to take the drugs or unwilling to participate in the study and thus they were failed to meet the inclusion criteria. A total of 372 (77.7%) patients who fulfilled the criteria were enrolled in the study, 143 (38.4%) of them did not finish the study and 229 (61.6%) patients finished the treatments of both regimens. Off 229 patients who finished the treatment, 86 of them were given INF-alfa plus ribavirin combination therapy and 143 were given Pegylated INF-alfa 2a plus ribavirin combination therapy.

Regarding the first regimen, a total of 86 patients who were given INF based treatment, forty six (54%) of them had end treatment response (ETR), and 22 (26%) of patients who had ETR relapsed. Though, 24 (28%) patients who received this regimen showed sustained virological response (SVR). Fifty patients who were given INF alfa based therapy were males, 21 (42%) of them had ETR. Thirty six patients who were given INF alfa based combination therapy were females, and 25 (69.4%) of them had ETR. The relationship between ETR to INF based therapy and gender was statistically significant CI=(1.5-3.5), (P=0.009). According to gender, only 10 (20%) male patients (n=50) had SVR, and 14 (38.9%) female patients (n=36) had SVR. The relationship between gender and SVR was statistically significant CI=(0.9-2.5) (P=0.016).

Regarding the second regimen, 98 (69%) of patients who were given PEG INF alfa 2a based therapy showed ETR, 47 (33%) of them relapsed. Though of this regimen 51 (36%) patients had SVR. A total of 88 patients who were given Peg INF alfa based combination therapy were males, 57 (68.8%) of them had ETR. Though 55 patients who were given Peg INF alfa based combination therapy were females, and 41 (74.5%) of them had ETR. SVR was also analyzed, accordingly 28 (31.8% n=88) male patients had SVR, and 23 (41.8%n=55) female patients had SVR CI=(0.5-1.2) (P=0.268).

The ETR and SVR of both regimens was determined according to different age group as shown in **Table 2**. A younger age patients were found to be responding better for both regimens used though Peg INF was more superior

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Table 2. The distribution of responders and non-responders to both therapeutic regimens according the age group among chronic HCV infected patients.

Age group	Responders(%)				Non-responders(%)			
	INF		PEG INF		INF		PEG INF	
	ETR	SVR	ETR	SVR	ETR	SVR	ETR	SVR
15-34	15	8	42	26	14	21	15	31
35-44	16	8	29	17	11	19	18	30
45-54	9	6	17	4	6	9	6	19
55-84	6	2	10	4	9	13	6	12
Total	46(56.7)	24(34.3)	98(65.8)	51(34.2)	40(39.2)	62(60.8)	45(32.8)	92(67.2)

ETR; end treatment response, SVR; sustained virological response.

in ETR & VSR CI = (3-4.3); CI= (0.4-2.0) (P = 0.626; P =0.105).

Monitoring of therapeutic regimens

Both liver function tests and viral load were monitored in this study, off 26 patients on INF based therapy who had ETR had normal ALT and 20 of them had raised abnormal ALT at diagnosis. Though,14 patients who had SVR had normal ALT level at diagnosis where as 10 patient who had SVR had abnormal ALT level at diagnosis. In PEG INF based group Where 57 patients who had ETR had normal ALT and 41 of them had elevated ALT. Furthermore, 25 patients of them who had SVR had normal ALT level at diagnosis where as 26 patients who had SVR had abnormal ALT level at diagnosis. The analysis of viral load showed that, in the first group based regimen 24 of patients who had ETR had low viremia at diagnosis (viral load less than 2 million and 22 of them had abnormal high viremia(viral load higher than2 million) at diagnosis. While 12 patients who had SVR had low viremia at diagnosis at diagnosis where as 12 patient who had SVR had high viremia at diagnosis. In the second group 61of patients who had (PEG INF based therapy) ETR had low viremia and 37of them had high viremia, While 33 patients who had SVR had low viremia at diagnosis where as 18 patients who had SVR had high viremia at diagnosis.

Role of HCV genotyping in monitoring therapy

The ETR and SVR of both regimens were correlated with the different HCV genotypes of the studied patients as shown in **Table 3**. Accordingly, different genotypes were reported among the patients. Those who received the first regimen(INF based therapy); 24 patients shown genotype 1; 33.3% of them had end treatment response (ETR), 13 patients with genotype 2; 69.2% had ETR, 21 patients with genotype 3; 52.4% had ETR, 28 of patients with genotype 4; 64.3% had ETR. On intention to treat 143 patients with the second regimen who were given Peg INF alfa2a based combination therapy. Off them 128 patients completed the course of treatment, 56 patients with genotype 1; 66.1% had ETR, 17 patients with genotype 2; 82.4% had ETR, 16 patients with genotype 3; 68.8% had ETR, 54 patients infected with genotype 4; 66.7% of them had ETR. Sustained virological response to INF alfa was measured by qualitative PCR after six months of end of the course of treatment only to responder, the end treatment response were recorded in 46 patients 24 of them the HCV RNA was undetected and 9 patients the HCV RNA were detected and 13 of responders were unknown 'patients missed the follow up', so 22 patients about 46.7% from responder did not have sustained virological response 'relapsed'. But on intention to treat about 27.9% had SVR and 62 patients about 72.1% did not had SVR. In patients who were given Peg INF combination therapy 98 of them had ETR; 51 of them had SVR, on intention to treat about 35.7% of patients had SVR. Ten of who had ETR had detected HCV RNA after six months about and 37 patients did not do PCR after six months, so about 48% of patients who had ETR relapsed.

Table 3. shows the correlation between SVR of both regimens and the different genotypes of HCV. Accordingly on intention to treat (INF based therapy) about 16.7% of genotype 1, HCV infected patients had SVR, 30.8% of genotype 2 infected patients had SVR, 23.8%of genotype 3 patients had SVR and 39.3% genotype 4 infected patients had SVR. In the second group and according to genotypes on intention to treat (PEG INF based therapy) genotype 1 infected patients about 32.1% had SVR and genotype 2 infected patients 35.3% had SVR, and about 43.7% of genotype 3 infected patients had SVR where as 37% of genotype 4 infected patients had SVR. **Figure 1** Illustrates the correlation between Viral response rates of different HCV genotypes and both End of Treatment Response (ETR) and sustained Virologic Response (SVR), according to intention -to -treat analysis.

Discussion

Hepatitis C virus infection results in chronic active hepatitis in more than 80% of infected patients; 20 to 30% of these patients develop progressive fibrosis and cirrhosis, whereas only approximately 10 to 20% of the infected people spontaneously eliminate the virus [**23**]. Treatment regimens for chronic hepatitis C have significantly improved during the last decade, resulting in higher sustained virological response (SVR) rates [**24**]. The dual anti-HCV therapy is based on administration

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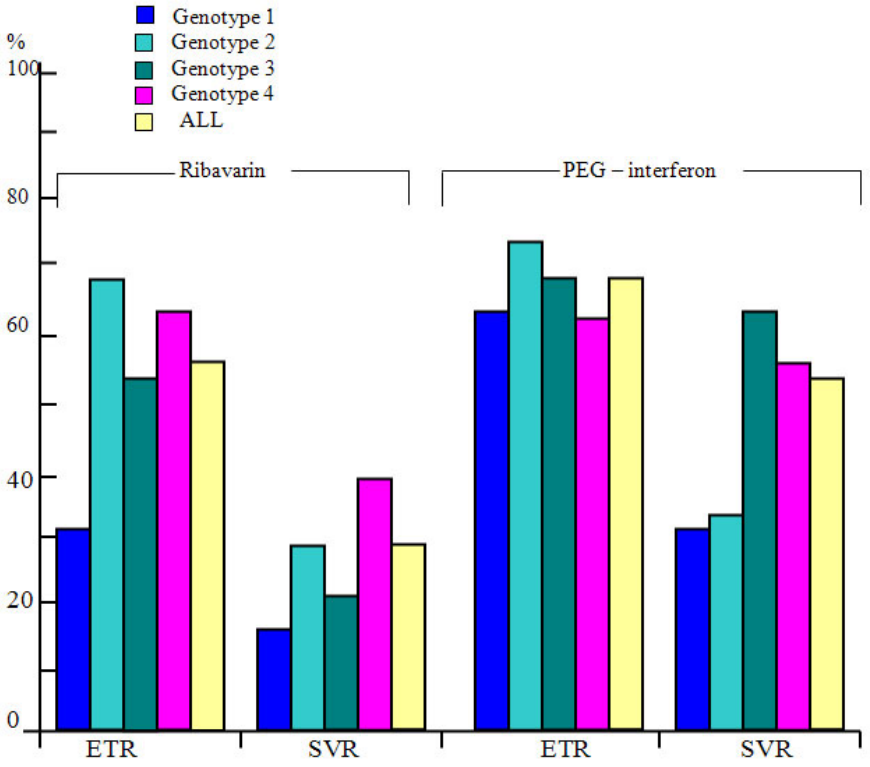

Figure 1. Viral response rates of different HCV genotypes; End of Treatment Response (ETR) and sustained Virologic Response (SVR), according to intention -to -treat analysis.

Table 3. The influence of HCV genotyping on the outcome response of both regimens studied.

Genotype/ subtype	Responders(%)				Non-responders(%)			
	INF		PEG INF		INF		PEG INF	
	ETR	SVR	ETR	SVR	ETR	SVR	ETR	SVR
Genotype 1a	0	0	9	5	3	3	2	6
1b	3	1	14	7	7	9	13	20
1 UC*	5	3	14	6	6	8	4	12
Genotype 2a	0	0	1	1	1	1	0	0
2b	0	0	1	0	0	0	0	1
2c	0	0	2	0	0	0	0	2
2a/c	0	0	0	0	1	1	1	1
2 UC	9	4	10	5	2	7	2	7
Genotype 3a	2	1	1	1	0	1	1	1
3 UC	9	4	10	6	10	15	4	8
Genotype 4a	4	3	4	1	2	3	4	7
4c/d	0	0	4	3	1	1	3	4
4UC	14	8	28	16	7	13	11	23
Total	46(65.7)	24(34.3)	98(65.8)	51(34.2)	40(39.2)	62(60.7)	45(61.7)	92(67.2)

*UC; Unclassified, ETR; End treatment response, SVR; sustained virologica response.

of long-acting pegylated alpha interferon (IFN) and ribavirin (RBV). Different factors have been evaluated as predictors of the sustained response to treatment, with controversial results [25]. In the present study we analyzed the efficiency of two regimens INF or PEG-INF alpha 2; either one was given in combination with RBV in treatment HCV infected patients.

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Off the patient treated with INF based regimen; 54% of them had ETR, 28% showed SVR and 26% relapsed, compared with PEG-INF based therapy where 69% showed ETR, 36% had SVR, and 33% who had ETR relapsed. This showed that Peg-INF has a better clinical outcomes compared to INF based regimen among Libyan patients infected HC Virus. Our data are in concordance with other studies that used the same regimens [26]. Discontinuation of HCV antiviral treatment was reported in both regimens used, it was 15 patients in Peg-INF and 10 patients in INF based regimen. Studies on HCV infected patients of Caucasian and African Americans had shown 21% a discontinuation rate, though in Japanese patients different rates were reported vary from 10.3% to 21% [27]. This is consistent with our result, though we could not analyze the effect on SVR of discontinuing in certain patients. Despite no specific correlation could be made between these studies, it's obvious that the tolerability of antiviral regimens used was satisfactory.

Different factors have been known to predict clinical response of antiviral-therapy among CHV patients these may include patient, viral and biochemical parameters [28,29]. Patient associated factors such as gender, age and the ethnic clan, have been studied by many investigators [2,30]. In this study we found a significant relationship between gender and both ETR and SVR in INF based therapy. Female patients had a higher SVR than male patients and the relationship was insignificant in PEG INF based therapy. Such results are compatible with other studies that revealed male sex had worse prognosis to therapy than female, that is may be because male patients have more ability to have liver cirrhosis [25].

The relationship between age groups and SVR were assessed in this study. A younger patients less than 40 years of age, were found to have a higher SVR rate compared with the older ones. This however, is an agreement with other studies, who reported that SVR rate in older patients was remarkably low at 17.4% compared to SVR rate in all patients included in study which was 36.0% these results were in disagreement with other studies carried in Pakistan where a significant relationship between age group and SVR as they found younger patients had higher SVR [31,32].

In this study we evaluated the biochemical parameters that have their influence on the SVR of both regimens used. Its well documented that most patients with an SVR normalize their serum ALT, AST shortly after discontinuing treatment unless other liver disease is present. The relationship between ALT and viral load level at diagnosis were insignificant in both regimens, some studies found inverse relationship between basal viral load and response to therapy [29]. Others did not found such relationship [33]. High ALT levels are correlates with liver cirrhosis but some studies revealed no relationship between response to therapy and ALT level before treatment [5,32]. This however is not the case of our study as those with live cirrhosis did not fit with patient selection criterion we applied.

Different viral related factors have been found to be involved in response of interferon treatment. Viral genotype, genetic diversity, viral load and kinetics where found to be among the most important ones involved. Recently, our group [34] and others [35,36] reported different rates of infection with different virus genotypes which was reflected on the viral response to the therapy used in treating HC infection. Interestingly, several studies have demonstrated that the chance to respond to IFN treatment is related to the baseline viral load. In this study strong association was found between viral load and ETR of patients treated INF based compared with those treated with Peg INF alfa2a therapy (P=0.976). Patients with a high viral load are less sensitive to the treatment than patients with a low viral load. Thus, patients with genotypes, low baseline viral load and RVR may be treated for a short period (*eg.,* 24 weeks), while patients with genotypes, high baseline viral load and without RVR may require longer period (*eg.,* 48 weeks) of treatment.

In this study according to genotypes and on intention to treat, ETR of patients treated PEG INF alfa 2a based regimen were superior to INF alfa based regimen in all genotypes though it was particularly significant in HCV genotype 1 ('*P* value=0.025'). These results were in agreement with the studies carried at University of Southampton [37]. Further more in both regimens HCV genotype 2, had a higher ETR than genotype 1 and 4 which same as previous study was carried in Cameroon [38]. However, both therapeutic regimens were less effective in patients infected with HCV genotype 1 and 4 although much higher ETR rates are reached in individuals infected with genotype 2.

Other studies have shown no differences in the clinical response of patients infected with HCV genotype 2 and 3, when they were treated with PEG INF alfa2a or INF alfa combination therapies [38,39]. The SVR of Peg INF based regimen was higher than INF based Regimen in all genotypes except for genotype 4 because as 11 patient infected with this genotype had ETR of Peg INF miss the follow up and thus excluded for the data analysis. Though, for those patients treated with INF based regimen, SVR was higher among patients infected with genotype 4 comparable to genotype 2 and 3 this may be related to discontinuation of therapy among the patients. The SVR in genotype 1 infected patients was the least in both regimens comparable to other genotypes. These results are similar to other studies carried in France on selected multiethnic patients from France, Egypt and other African countries who were treated with Peg INF alfa 2a based regimen [26,39]. In their study the selected patients were French and Egyptian and other African who had HCV genotype 4 infection on Peg INF alfa 2a they found. SVR was variable according to the ethnicity as it was 54% among Egyptian, 40.3% in French patient and among Africans it was 32.4% [40]. The relationship between HCV subtypes and ETR and SVR were also studied. No significant relationship was found, particularly with patients with HCV genotype 1a and 1b.

Our studies are in accordance with those carried by Zeuzem; who did find heterogeneous virological response rates to interferon- based therapy in patients with chronic hepatitis C based on genotypes and subtypes of HCV [37,41]. Hence then virus clearance rates are variable different depending on viral genotypes and that could be used to monitor HCV therapy.

Despite the limitations that this study facing due to the inability of some patients to finish the due course of the therapy and the discontinuation of the regimens among others. Our results highlights the importance of monitoring antiviral therapy and the factors that influence such therapy among treated patients.

In conclusion, we have found that Responsiveness to hepatitis C virus therapy is variable according to the different regimens used. Certain factors such as gender, age, viral load and genotypes influence viral response rate. Furthermore, genotype 1 and 4 were more resistant comparable with other genotypes. Therefore, New drug therapies such as antiviral protease and antipolymerase should be combined with the ongoing therapy both to increase SVR among non responsive patients and reduce the duration of treatment particularly of those who were infected with resistant genotypes.

Competing interests
The authors declare no relationship (commercial or otherwise) that may constitute a dual or conflicting interest.

Authors' contributions
Daw MA; A leading expert in Microbial- epidemiology and Antimicrobial therapy, Designed the study, constructed the Manuscript and analyzed the data. HME; Followed the patients and collected the data. AAD; Analyzed the data & read the MS. MMA; Assessed the clinical study, analyzed the data and read the MS.

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