HARVONI VERSUS 3D REGIMENS OUTCOMES AMONG HCV INFECTED PATIENTS VISITED KURDISTAN CENTER FOR GASTROENTEROLOGY AND HEPATOLOGY (KCGH).

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ABSTRACT

Background

Approximately 3% of the world's population is infected by the Hepatitis C virus (HCV), and more than 2/3rd of patients have chronic hepatitis. The recent revolutions in HCV treatment have led the World Health Organization to target its elimination as a public health threat by 2030.

Objectives

To evaluate and compare the efficacy of two therapeutic regimens in HCV management.

Patients and Methods

This is a comparative prospective clinical study was conducted on 88 patients with HCV at Kurdistan Center for gastroenterology and hepatology (KCGH) in a teaching hospital in the Sulaimaniah City-Kurdistan region of Iraq from January 2020 to December 2020.

The patients were divided into two groups; one group received Harvoni (sofosbuvir/ledipasvir), and the other group was given three-drug regimens (Exviera plus Viekrax (ombitasvir/paritaprevir/ritonavir plus dasabuvir) for 12 weeks. The collected data before and after treatment were analyzed through Statistical Package for the Social Sciences (SPSS version 26.0).

Results

The patients' mean age was found to be 38.6 years. Males were accounted for a more significant number of the patients (55.7%). The two groups were not significantly different in terms of age, gender, nationality, occupation, BMI, DM, and risk factors (P-value>0.05). But a significant difference was seen between them in terms of their initial glomerular filtration rate (p-value=0.003). In addition, the patients' gender, age, and HCV genotype were not significantly correlated with their sustain virology response (SVR). Also, a significant difference was observed between the two groups in terms of SVR after three months of treatment, such that more patients who received Harvoni achieved SVR. Moreover, there was a significant relationship between the initial fibrosis stage and the patients' SVR to the treatment (p-value=0.01).

Conclusion

Compared to the 3 D regimens (Exviera plus Viekrax), Harvoni was more effective for treating patients with chronic HCV.

Keywords: *HCV, Harvoni, Three-drug regimen, KCGH .*

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INTRODUCTION

Hepatitis C virus (HCV) is one of the major causes of mortality from liver cirrhosis, hepatocellular cancer (HCC), and many associated extrahepatic complications; the global burden was estimated to be 71 million individuals in 2015 [1]. Contrary to the past decade, now we know much more about pathophysiology and detrimental effects of HCV-related diseases, as well as considerable advances in diagnostic procedures and improvements in therapy and prevention, make it possible to put a strategy to eliminate hepatitis C as a significant public health threat, as WHO proposed this target by 2030 [2].

Hepatitis C virus (HCV) is a small, single-stranded, enveloped RNA of the genus Hepacivirus of the family Flaviviridae with an extraordinarily high degree of genetic diversity, which creates a significant challenge for the development of HCV vaccines [3]. HCV strains are classified into six major genotypes (1-6) based on phylogenetic and sequence analyses of whole viral genomes [4]. Globally, genotypes one and 3 are the most common genotypes that account for (46.2%) and (30.1%) of HCV-infected cases. Genotypes 2, 4, and 6 are responsible for the remaining (9.1%), (8.3%), and (5.4%) cases, respectively, while genotype five is estimated to be responsible for <1% of all HCV cases [5]. Although approximately 80-85% of cases of HCV infection become chronic, with significant clinical consequences such as the increased risk of cirrhosis and HCC, this treatment aims to eradicate the virus, prevent disease progression and complications, and transmit the disease to others[6]. The best effective treatment is sustained virology response (SVR).

Sustained virology response is defined as the absence of detectable viral RNA in serum 12–24 weeks after the end of treatment [7]. SVR corresponds to a cure of the HCV infection, as late relapse occurs in less than 0.2% of cases beyond six months of follow-up [8]. In addition, SVR is generally associated with normalization of liver enzymes and improvement or regression of liver inflammation and fibrosis, and improvement in liver function [9].

The risk of HCC and liver-related mortality is significantly reduced but not eliminated in patients with cirrhosis who clear HCV compared to untreated or non-SVR patients [10]. Since 2011 when the first generation of new direct-acting antivirals (DAAs) was approved to be given in combination with interferon (INF) and ribavirin, they have been associated with higher SVR, fewer relapses, shortened treatment duration, but increased side effects [11]. During the last few years, the advent of new DAAs has replaced INF based therapy, and improved treatment efficacy of HCV infection, with SVR, rates greater than 95% and an excellent safety profile even in patients who were previously considered difficult to treat (patients with cirrhosis, HCC, co-infected with HIV, or extrahepatic manifestations such as cryoglobulinemia vasculitis) [12]. Currently, the pan-genotypic DAAs are approved by WHO, the European Association for the Study of the Liver (EASL), and the American Association for the Study of Liver Diseases (AASLD) are available in most markets for the treatment, which opens a gate for the public health response to HCV infection with simplified treatment regimens, an omission of cost of genotyping and need for frequent laboratory monitoring [13].

PATIENTS AND METHODS

This randomized comparative prospective clinical study was conducted in Kurdistan Center for gastroenterology and hepatology (KCGH), in a teaching hospital in Sulaimaniah City/Kurdistan region - Iraq from January 2020 to December 2020; a total number of 88 participants who fulfilled the inclusions criteria (age above 12 years, non-pregnant ladies) were submitted for the data analysis.

The diagnosis of HCV infection relied on a positive anti-HCV antibody test by enzyme-linked immunosorbent assay (ELISA) with confirmation of active infection by detection of HCV-RNA by reverse transcription-polymerase reaction test (RT-PCR) by Cobas Amplicor HCV test, version 2.0 (Roche Molecular System, Branchburg, NJ) with the lowest limit for detection of 10-15 IU/mL.

The participants were divided into two groups; group A (58 participants) were treated with Harvoni (sofosbuvir/ledipasvir) for 12 weeks, and group B (30 participants) with three-drug regimens (Exviera plus Viekrax (ombitasvir/paritaprevir/ritonavir plus dasabuvir) for 12 weeks. The two groups were equally distributed and available in our centre. Thorough clinical history and examination of the participants were undertaken, and all records of patients were reviewed, including; sociodemographic data (such as age, gender, residency, nationality, marital status, and occupations risk factors for HCV infections (traumatic medical procedures including surgery, dental care, blood transfusions, dialysis, sexual contacts, and prisoner). By using WHO

body mass index classification for general population participants classified in to normal weight (BMI = 18.5 -24.9 kg/m2), overweight (BMI=25-29.90 kg/m2) and obese (BMI≥30 kg/m (2).

History of prior antiviral therapy other than the regimens used in this study, chronic medical illnesses (such as diabetes, hypertension, renal impairment, hemoglobinopathy, medications history), laboratory tests (such as HCV RNA, HCV genotypes, liver enzymes (ALT, AST), hepatic fibrosis and steatosis assessed by either ultrasound elastography or fibroscan, renal function test, and complete blood count) were entered for the analysis at the initiation of treatment and repeated at the end of treatment and 12 weeks post-treatment. All participants were informed about documenting and reporting any suspected drug adverse effects to the investigator at regular monthly follow-up or telephone contact.

Data analysis

Data required for analysis entered using Statistical Package for Social Sciences (SPSS version 26) was used. Descriptive statistics are presented as (mean ± SD), frequencies and percentages. Chi-square was used for categorical variables. One-way ANOVA analysis was used to compare more than two means. Statistical significance was considered whenever the P-value was less than 0.05.

Ethical approval

Ethical approval of the current study was obtained by the research ethics committee of Kurdistan Board of Medical Specialities; code number (528) release date; Mar 4 2021. The aim of the study and its impact on our clinical practice has been explained to the participants, and their involvement was voluntary, and both verbal and written informed consent was obtained from them. Furthermore, the confidentiality of the collected data was guaranteed

RESULTS

The present study showed that the age range of the participants was between 12 to 80 years, with a mean age of 38.60±18.39 years. It was seen that 49 of the participants (55.7%) were males, and 39 (44.3%) were females, with a male-to-female ratio of 1.26:1. The two groups (Harvoni Group and 3D regimen Group) were not significantly different in terms of their age and gender (p-value for age=0.16) and (p-value for gender=0.5).

Regarding their nationality, 64 (72.7%) were Kurdish, and 24 (27.3%) were Arabic, and there was not a significant difference between the two groups regarding their nationality (p-value=0.054). In terms of their occupation, 30 (34.1%) were self-employed, 27 (30.7) housewives, 16 (18.2%) students, and 15 (17.0%) governmental employees, and no significant difference was observed between the two groups in this regard (p-value=0.32).

It was observed that 10 participants (11.4%) were overweight and 7 (8.0%) were obese, and the two groups were not significantly different in this regard (p-value=0.4). Regarding their medical diseases, 15 (17.0%) had diabetes, and 15 (17.0%) had chronic kidney disease. The two groups were not significantly different in diabetes mellitus (p-value=0.59). A significant difference was observed between the two groups regarding the initial glomerular filtration rate (GFR) (p-value=0.003). The most common source for HCV infection was via invasive medical procedures such as surgery, accounting for 49 cases (55.7%). Other risk factors included hemodialysis, repeated blood transfusion, dental care, and imprisonment accounting for 15.9%, 14.8%, 11.4%, and 2.3%, respectively. The two groups were not significantly different regarding the risk factors (p-value=0.08), Table 1.

Regarding the patients' genotype, the results showed that most of them were genotype 1 (69.32%) and genotype 4 (22.73%), and the rest (18%) were genotype 2, 3, 5, and 6

No significant associations observed between SVR) after 3 months following the treatment and the patients' gender (p-value=0.28), age (p-value=0.52), and genotype (p-vale=0.35). While SVR and their nationality were significantly correlated (p-value=0.02), Table 2.

The results also demonstrated there was a significant difference between the two groups in terms of SVR P-value 0.02), such that SVR was achieved by 91.4 of the patients in group A (Harvoni), while it was achieved by 73.3 of group B (3-drug regimen), Table 3.

The results revealed a significant relationship between the initial fibrosis stage and the patients' SVR to the treatment (p-value=0.01). In addition, there was a significant statistical difference, Table 4.

According to the results, no significant relationship was seen between the two regimens (Harvoni and 3D regimens) and their side effect profiles (p-value=0.01). There was no significant statistical difference. Table 5.

Table 1. Sociodemographic and general characteristics distribution of the participants .

Variables		Group A (Harvoni) No. (%)	Group B (3D) No. (%)	P-value
Age group(year)	12-24	20 (34.0)	8(26.7)	
	25-49	19(33.0)	16(53.3)	**0.16**
	≥ 50	19(33.0)	6(20.0)	
Gender	Male	27 (46.6)	18 (60.0)	**0.5**
	Female	31(53.4)	12 (40.0)	
Nationality	Kurdish	46 (79.3)	18 (60.0)	**0.054**
	Arabic	12 (20.7)	12 (40.0)	
Occupation	Housewife	20 (34.5)	7 (23.3)	
	student	12 (20.7)	4 (13.3)	**0.32**
	Governmental employee	10 (17.2)	5 (16.7)	
	Self-employee	16 (27.6)	14 (46.7)	
BMI	Normal	48 (82.8)	23 (76.7)	
	Overweight	7 (12.1)	3 (10.0)	**0.40**
	Obese	3 (5.1)	4 (13.3)	
Diabetes Mellitus	Absent	49 (84.5)	24 (80.0)	**0.59**
	Present	9(15.5)	6 (20.0)	
Initial GFR	Normal	53(91.4)	20(66.7)	**0.003**
	Renal impairment	5(8.6)	10(33.3)	
Risk factors	Invasive medical procedures	43(74.1)	12(53.3)	
	Blood transfusion	9(15.5)	4(13.3)	**0.08**
	Dialysis	5(8.6)	9 (30.0)	
	Prisoner	1(1.7)	1 (3.3)	

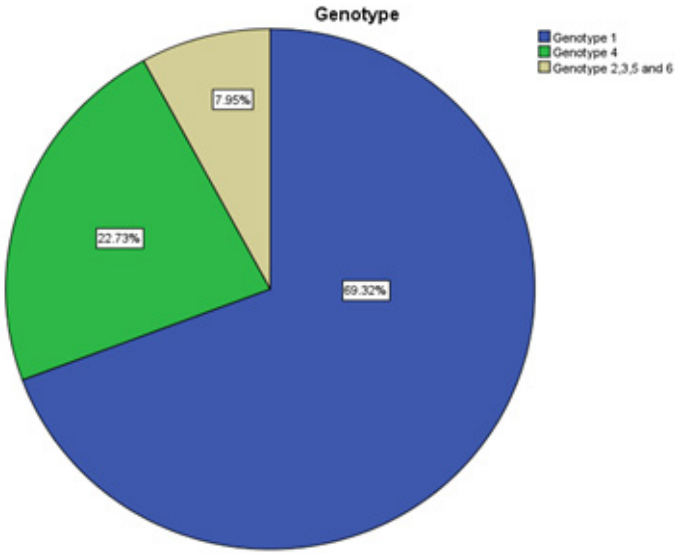

Figure 1. Genotype distribution among the patients.

Table 2. The response rate according to gender, age groups, nationality, and genotype prevalence between the two drug regimens.

Variables		Sustain virology response (SVR) at three months after treatment		P-value
		Achieved No (%)	Failed to achieved No (%)	
Gender	Male	40 (81.6)	9 (18.7)	**0.28**
	Female	35 (89.7)	4 (10.3)	
Age groups(year)	12-24	23 (82.1)	5 (17.9)	
	25-49	29 (82.9)	6 (17.1)	**0.52**
	≥ 50	23 (92.0)	2 (8.0)	
Nationality	Kurdish	58 (90.6)	6 (9.4)	**0.02**
	Arabic	17 (70.8)	7(29.2)	
Genotype	Genotype 1	50 (81.9)	11 (18.1)	
	Genotype 4	18(90.0)	2 (10.0)	**0.35**
	Genotypes 2,3,5 and 6	7 (100.0)	0 (0.0)	

Table 3. The difference between the two groups in terms of sustain virology response (SVR) at three months after treatment.

Regimen	Sustain virology response (SVR) at three months after treatment		P-value
	Achieved No (%)	Failed to achieved No (%)	
Group A (Harvoni)	53 (91.4)	5 (8.6)	0.02
Group B (3 D regimen)	22 (73.3)	8 (26.7)	

Table 4. The relation between the fibrosis stage and response to the treatment.

Initial fibrosis stage	Achieved SVR	Failed to achieve SVR	P-value
Stage 0	31(73.8)	11(26.2)	
Stage 1-2	24 (100.0)	0 (0.0)	0.01
Stage 3-4	20(90.9)	2 (9.1)	

Table 5. The relation between side effect profile and the two drug regimens.

Adverse events	Regimen		P-value
	Group A (Harvoni)	Group B (3 drug regimen)	
No side effect	41 (70.68)	20(66.6)	
Gastrointestinal upset, Nausea, Vomiting, Anorexia	8 (13.79)	7 (23.3)	
Neuropsychiatric headache, fatigue, angriness, and sleep disturbance,	7 (12.06))	1 (3.33)	**0.32**
Hematologic anaemia, thrombocytopenia	1 (1.72	2 (6.66)	
Dermatologic skin rash	1 (1.72)	0 (0.0)	

DISCUSSION

The present study results demonstrated that there was no significant difference between the two groups in terms of general characteristics of participant distribution except for the renal impairment as they were assigned to receive three-drug regimens due to safety issues of Harvoni on eGFR. This concern is supported by the results of Soeiro et al., who reported a significant drop in initial GFR during treatment in all study groups; however, this decrease was slight and reversible after the consumption of Harvoni was stopped [14]. The most prevalent genotypes in the present study were genotypes 1 and 4, with a percentage of 69.32% and 22.73%, respectively.

This result is consistent with a previous study done in 2017, which reported that genotype one had been highly prevalent, followed by genotype 4 (67.2% and 27.6% respectively) and another study in 2009 again in Sulaimaniah-Iraq which reported that revealed 87% of study patients had genotype 1 [15, 16]. This finding is in keeping with the recent change in genotype prevalence among Iraqi chronic HCV patients as claimed by Abdel Wahab et al., who conclude that across six years of records, HCV genotype 4 was the most prevalent among Iraqi chronic hepatitis patients (46.68%), then genotype 1 (37.12%) but, since 2017 there is a notable change in HCV genotypes distribution, where the genotype one predominantly found (52.63%) [17].

A recent epidemiologic systematic review and meta-analysis in Iran done by Mahmud, S. et al. revealed that Genotype 1 was the most frequent circulating strain at 58.2%, followed by genotype three at 39.0% [18]. These findings are contrary to studies done In the Middle East and North Africa (MENA) region, where they declare that genotype 4 is most prevalent [19]. The present study shows the most common source for HCV infection was as a result of invasive medical procedures, including surgery and dental care in both groups (74.1% for group A, and 53.3% for group B); followed by dialysis and blood transfusion, these findings are in line with study done in Al-Nasiriyah governorate of Iraq by Hassan Abd Ali Khudhair. et al. found that Blood transfusion 15.4%, renal dialysis (6.6%), and health care workers (5.8%) were significant sources of infection [20].

In the present study, there were no significant associations between the participants' age, genotype, gender, and SVR at three months following treatment. In this regard, Saab S, Park SH, Mizokami M, et al. found that SVR at 12 weeks was achieved by 97% of participants younger than 65 years and 98% of participants aged 65 years older with similar side effect profiles in the two age cohorts [21]. Concerning the gender, Simoes P. et al. revealed that SVR was significantly lower in women than in men (24% vs 59%; $p < .01$), which persisted even after adjusting for age, race, genotype, prior treatment status, duration of therapy, and stage of fibrosis [22].

The difference between the results of this study and mentioned study may be explained in many points such as; differences in drug regimens, age categorization of participants, the difference in HCV genotypes between our study and others as we included all genotypes, Also biologic, non-biologic and racial factors may differ among studies which influence in part the response rate to the treatment. For example, Su et al. reported lower rates of SVR to INF-based therapies for chronic HCV infection among the Black race and Hispanic ethnicity.

In comparison, higher SVR rates were observed among the Asian race than white patients; they also observed high SVR rates to DAA in most studied racial groups (Asian/Pacific Islander/American Indian/Alaska Native, Hispanic, Black, and White patients). However, after adjusting baseline characteristics, Hispanic ethnicity and the black race remained independent predictors of treatment failure [23].

In the current study, there is a significant correlation between SVR and the nationality of participants, in which being Kurdish is associated with a higher SVR rate (P-value. 0.02). According to the results of a systematic review of three sizeable pivotal phases 3 trials (ION-1, ION-2, and ION-3) were designed to assess the efficacy and various durations of Harvoni with or without ribavirin in patients with genotype one chronic HCV infection, the overall SVR12 ranged from 93% to 99% in all treatment groups in all three trials regardless the presence or absence of cirrhosis, prior treatment experience or the duration of treatment whether 12 weeks or 24 weeks [24]. Inconsistent with this, our study shows SVR12 to the Harvoni was 91.4% regardless of fibrosis stage or prior treatment exposure. It was significantly higher than the three-drug regimens, 73.3 % (P-value 0.02). Ferenci P. et al. did a pooled analysis of post-marketing observational studies from 13 countries on the efficacy and safety of 3 drug regimens (Exviera/ Viekrax ± ribavirin). They found that in patients with HCV GT1a, GT1b or GT4, SVR12 rates were 93%, 97% and 94% [25].

Our study's lower SVR-12 to 3 drug regimen may be explained firstly by; 1/3rd of participants were on twice-weekly based dialysis, which continuously exposed them to HCV from the contaminated machine. Secondly, we included all genotypes to receive three-drug regimens. Lastly, limited access to ribavirin as we haven't it in our centre to provide it with three drugs and about half of the patients could not afford it outside. In regards to the relation between fibrosis stage and SVR 12 in both groups together, this study has shown significant association such that100% of patients with stage 1-2 cirrhosis achieved SVR, while 90% of patients with advanced fibrosis stage 3-4 achieved SVR 12. These findings are comparable and nearly similar to the conclusion of the ION-1 trial results, as mentioned earlier [24].

Pooled data analysis from the aforementioned ION-1, ION-2, and ION-3 trials revealed overall rates of adverse effects (AEs) were high among all treatment groups in the three trials regardless of RBV or duration of treatment, ranging from 67% to 90%, AEs were mostly mild to moderate in severity, The most common AEs reported for LDV/SOF regimens included fatigue, headache, and nausea (all > 10%) [24].

In line with this, the present study showed that (29.3%) patients developed AES. The most common drug-related AEs were gastrointestinal (GI) upset in the form of anorexia, nausea, and vomiting was observed in 13.7%. Neuropsychiatric AEs included headache, fatigue, insomnia, angriness in 12% of patients in the Harvoni group. Most of these side effects were mild and did not warrant any changes or stopping treatment.

One (1.7%) patient had skin rash with an itch, which was disappeared spontaneously after completing the treatment, one (1.7%) patient developed anaemia with a 1-2 gm drop in haemoglobin compared to before the treatment records during the treatment period and gained 1 gm haemoglobin after three months post-treatment. Ferenci P. et al. reported (26.2%) of participants developed ≥1 treatment-emergent AE to 3 drug regimens. The most common side effects were fatigue (6.4%) and anaemia (5.2%), serious AEs occurred in (3.4%), with severe anaemia (0.4%), hepatic failure (0.2%), HCC (0.1%) and jaundice (0.1%) being the most frequently reported serious AEs. The incidence of anaemia was most commonly reported in patients who received ribavirin [25].

In this regard, three-drug regimen groups in the present study showed (33.4 %) of patients reported drug-related AEs, with the most common AEs being mild GI upset (23.3%) in the form of anorexia, nausea, occasional vomiting, and mild anaemia (6.6%), one (3.3%) reported fatigue, which coincided during the treatment period and could not be explained by other causes; no patients said new-onset jaundice or showed deranged liver enzymes while receiving treatments. As mentioned earlier, 1/3rd of patients in this group were on dialysis due to ESRD.

In addition, many had cirrhosis and diabetes with multiple comedications; this may explain prevalent GI AEs and anaemia.

In conclusion, Harvoni (Sofosbuvir/Ledipasvir) is effective and safe for chronic HCV infection with higher SVR12 than the three-drug regimens. This study highlighted that Kurdish patients responded better than Arabic patients, although this issue needs a more extensive analysis searching for the factors behind this difference. In addition, a more extended period of follow-up after initial recovery from chronic HCV infection may be needed to assess relapse and regression of fibrosis and other complications of the virus and compare it to those who failed to achieve SVR to realize the cost-effectiveness of HCV eradication.

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