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Treatment outcome of chronic hepatitis C virus infected patients and experience with direct acting agents from Ethiopia: Retrospective study

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Abstract

Background: Hepatitis C virus is a multisystem disease with substantial morbidity and mortality. The genotypic distribution of the virus and treatment outcome with direct acting agents are variable geographically.

Method: A retrospective study was conducted to assess treatment outcome of Hepatitis C infected patients treated with direct agents at Tikur Anbessa Specialized Hospital and Adera Gastrointestinal Specialty clinic from January 2018 to January 2020. A total of 84 patients were included. The data was analyzed by using the latest SPSS version 26.

Result: A total of 84 patients were included with a mean age of 49±10.6 years. Diabetes and Hypertension were the commonest comorbidities. Majority of the patients were found to be infected with genotype. Seventy-seven (91.7%) patients were treatment naïve and 34(40.5%) had evidence of liver cirrhosis. Overall sustained virologic response at 12 weeks was achieved in 76 (90.5%) patients. The virologic response occurred in 93.5% non-cirrhotic and 83.5% of cirrhotic patients. The presence of fibrosis was found to be associated with non-response to therapy. Fatigue and nausea were the commonest side effects and life-threatening complications were not reported.

Conclusion: The current study found treatment of chronic HCV infected Ethiopian patients with DAAs resulted in 90.5 % SVR12 rate with minimal safety concerns. The study also found, non-cirrhotic patients achieved higher rates SVR12 than cirrhotic patients and high APRI score negatively affect treatment outcome.

Keywords: hepatitis c virus; direct antiviral agents; sustained virologic response

Introduction

Background Information

Hepatitis C virus (HCV) is enveloped RNA virus belonging to the genius Hepacivirus in the family of flaviviridae. Based on genetic sequencing HCV has eight genotypes with variable geographic distribution and response to antiviral therapy [1]. Genotype 1 is the commonest type worldwide with a greater prevalence in USA, Europe and Australia followed by genotype 3 which is predominant in the southern and southeast Asia [2]. Genotype 4 on the other hand is the main infectious cause in northern, central and east Africa including Ethiopia [2-5].

According to the World Health Organization (WHO) estimate there are 130–150 million people are chronically infected with HCV worldwide. Having 11 million people infected with chronic HCV, its prevalence in Africa is around 1%. Viral hepatitis is responsible for an estimated 1.4 million deaths per year which is comparable to that of HIV and tuberculosis. HCV is also a growing cause of mortality among people living with HIV. About 2.9 million people living with HIV are co-infected with hepatitis C virus [6, 7].

A systemic review and met analysis done in 2016 on 24 papers here in Ethiopia showed the overall pooled prevalence of anti-hepatitis C virus antibody (anti-HCV) as 3.1% (95%CI: 2.2–4.4). It also showed that people who are HIV positive have a higher anti- HCV antibody than HIV negative people (5.5%, 95%CI: 3.8–7.8%, p = 0.01) [8]. The virus is transmitted by several means, mainly parenterally. Injectable drug users have the highest risk of getting the infection, where-as transmission through unsafe medication injection with poor infection prevention protocol leads to transmission in health care facilities. The other possible ways of transmission are blood transfusion, vertically and sexually especially in men who have sex with me [9, 10].

Chronic HCV infection is a systemic disease with both hepatic and extrahepatic complications.

Worldwide it remains to be among one of the leading causes of cirrhosis, hepatocellular carcinoma and Liver transplantation [11, 12]. It is associated with an increased risk of hepatic related and all-cause mortality as well as morbidity [13]. The extrahepatic manifestations include increased risk of diabetes, depression, cardiovascular, neurologic, renal and variable immune mediated disorders [14-16].

In the previous decades interferon (IFN) and ribavirin was the mainstay of HCV treatment. Both agents have indirect antiviral activity and achieve a lower SVR rate of 40 to 50% with significant toxicity profile. Recent introduction of Direct antiviral agents (DAAs) has revolutionized the treatment outcome of patients with HCV. They are better tolerated and achieve high SVR with a shorter duration of therapy [17].

The newer agents directly act on viral replication and target three non-structural proteins. These targets include NS3/4A, NS5A, and NS5B. NS5B inhibitors include sofosbuvir and dasabuvir. NS5A inhibitors include ledipasvir, daclatasvir, velpatasvir, and elbasvir, and ombitasvir. NS3/4A inhibitors that include boceprevir, telaprevir, simeprevir, asunaprevir, and grazoprevir [18]. Although there are pangenotypic direct acting antivirals, the treatment of HCV infection is tailored by the specific genotype and a combination of DAAs from different class is recommended. Currently there are three pangenotypic DAAs combinations are approved including an eight-week course of glecaprevir-pibrentasvir and a 12-week course of sofosbuvir-daclatasvir and sofosbuvir-velpatasvir [19].

Because of the global burden of HCV and the availability of highly effective drugs for HCV, in 2016 the WHO launched a program to eliminate HCV as a public health threat by 2030 [7]. However, the limited real-world data on effectiveness of DAAs combined with the cost and availability of this drugs in low socioeconomic countries like Ethiopia have a negative impact on achieving this goal.

Treatment outcome of HCV is affected by the viral genotype and subtype among other factors. To date, there is limited study in Ethiopia which assessed the efficacy of DAAs even though viral genotype is different from the west. By addressing this knowledge gap, we believe this study will be valuable for both clinicians and policy makers. It will also be a baseline study for future researches.

Methodology and Material

Study Design and Setting

A retrospective study was conducted to assess treatment outcome of chronic HCV infected patients treated with DAAs at Tikur Anbessa Specialized Hospital and Adera Gastrointestinal Specialty clinic from January 2018 to January 2020. The study was conducted at two HCV treatment centers in Addis Ababa Ethiopia. These are TASH and Adera internal medicine specialty clinic. TASH is one of the oldest and largest tertiary university hospitals located in the Central part of Addis Ababa Ethiopia. In both TASH and Adera clinic, chronic HCV infected patients are managed with the most experienced consultant gastroenterologists available in Ethiopia.

Study population

All patients who had have follow up at the adult GI follow-up unit were used as source population and those who were treated with DAAs for HCV infection were the study population.

Inclusion criteria

- Age >/=18 years
- Chronic HCV infected patients treated with DAAs during the study period.

Exclusion criteria

- Incomplete medical record

Sample size of 84 was calculated by a single population proportion formula using a 95 % confident interval (CI), 5% margin of error, and SVR12 rate of 96% from studies done in Egypt which has similar genotypic distribution of HCV like Ethiopia [20]. Systematic random sampling was used to select patients.

Data collection method

A pretested structured questionnaire was used to collect data. Data was collected from patients' chart and electronic records. Data was collected by the principal investigator and medical interns. Patient chart, electronic medical recording and pharmacy registries were used for data completeness. During data collection, continuous follow up and supervision was done by the principal investigator. Finally, the collected data was checked for completeness before execution of any data entry process.

Operational definitions

Sustained Virologic response (SVR12): Is defined as undetectable (< 15 IU/ml) HCV RNA level 12 weeks after end of therapy with DAAs.

DAA induced ADR: defined as patient reported or lab-oratorically detected abnormalities which are labeled as DAA induced side effects by the treating physician. Treatment failure: defined as the presence of detectable (> 15 IU/ml) serum HCV RNA 12 weeks after completion of DAAs.

Data analysis procedures

Data was entered into the latest SPSS version 26 manually. Data was analyzed and result summarized by using descriptive statics. Continuous variables are reported as mean and standard deviation. fisher's exact test was used to check for any association between the categorical variables and considered to be statistically significant when the p value is below 0.05. logistic regression model was used to assess for any association between continuous independent variables and the dependent variable. Confidence interval and power are set at 95 % and 80 % respectively. ratio with a 95 % confidence interval is used to determine the presence, strength, and direction of association between covariates and the outcome variable.

Ethical Clearance

Before conducting the study, the study proposal was submitted to the department of internal medicine and ethical clearance was issued by the institutional review board of Addis Ababa University and Adera Hospital. Because of the retrospective nature of the study written consent was not required. Anonymity of the study subjects remained confidential. The study was conducted in accordance with the Helsinki Declaration of the 1975.

Result

Sociodemographic and clinical characteristics

A total of 84 participants were included in the final analysis. Among them, 47 (56 %) were females and the mean age was 49 ±10.6 years. Forty-five (53 %) of patients were treated at Adera Specialty clinic.

More than third (36.9 %) of patients have one or more medical comorbidities. Diabetes mellitus and hypertension were diagnosed in 14 (16.7 %) and 18 (21.4 %) of patients. Seven (8.3 %) and 3 (3.6 %) of the participants have Human Immunodeficiency Virus (HIV) and Chronic Hepatitis B Virus (CHB) Coinfection respectively. Nine (10.7 %) patients had concomitant diagnosis of Fatty liver disease.

Seventy-seven (91.7 %) of patients enrolled in this study were treatment naïve. Among those who received prior treatment, four patients with Sofosbuvir-Ledipasvir (SOF/LED) regimen, one with interferon-ribavirin, one with Sofosbuvir-Daclatasvir (SOF/DCL) regimen and one patient with both direct acting antiviral and interferon-based regimens.

The Sociodemographic and clinical characteristics are shown in Table 1 below.

Table 1 : Sociodemographic and clinical characteristics of chronic HCV infected patients treated with DAAs at TASH and Adera specialty clinic from January 2018 and January 2020 G.C.

Variables		Frequency	Percent (%)
Age in Years	20-35	9	10.7
	36-50	35	41.7
	51-65	34	40.5
	>65	6	7.1
Gender	Male	37	44.0
	Female	47	56.0
Treatment Center	Tikur Anbessa	39	46.4
	Adera	45	53.6
Address	Addis Ababa	66	78.6
	Oromia	4	4.8
	Amhara	7	8.3
	SNNRP	4	4.8
	Others	3	3.6
Medical Comorbidities	Diabetes	14	16.7
	Hypertension	18	21.4
	Hepatitis B Virus	3	3.6
	HIV	7	8.3
	Other	7	8.3
Previous Antiviral Treatment	Naïve	77	91.7
	Experienced	7	8.3

Baseline laboratory, virologic and imaging characteristics

Noninvasive assessment of liver fibrosis using APRI (AST to Platelet ratio) score was done for 74 patients before initiation of therapy. Of these patients, 45 had value ≤1 and 29 had value >1 which is reported to fairly correlate with cirrhosis based on previous studies. Forty-three (51.2 %) of the 74 patients had APRI score more than 0.7 which correlates with F2-F4 fibrosis in patients with Chronic HCV infection [21].

Fifty-one (60.7 %) of the 84 patients enrolled in this study have their hepatitis C virus genotype known before administration of DAAs. The most frequently found genotype was genotype 4; detected in 39 (76.4 %) patients, followed by Genotype 1 (n= 7, 13.7 %) and Genotype 2 (n= 3, 5.9 %) genotype 3 and 5 accounted for 1 (1.9 %) patient each. Viral subtype was documented for 13 patients, of these, five had subtype 4e, two had subtype 4a/c/d, two had subtype 2a/c, one patient subtype 2c and three patients with subtype 1a/b, 1b and 1g each. Pretreatment HCV Viral load value ranges from 450 to 17 million copies, with average viral RNA level of 2.7 million.

Abdominal Ultrasound was documented for (n=80, 95 %) patients, and 39 (46 %) had normal abdominal sonography report, features of early or late cirrhosis was documented in (n=34, 40 %) of patients. Only six patients had documented fibro scan and three had F4 fibrosis. Sixteen (19 %) patients had upper gastrointestinal endoscopy, of whom 13 (15.5 %) had different grades of esophageal varices, and 3 had normal endoscopy report.

Laboratory and Imaging characteristics of the study participants is shown in Table 2 below.

Table 2: Laboratory and Imaging characteristics of chronic HCV infected patients treated with DAAs at TASH and Adera specialty clinic from January 2018 and January 2020 G.C.

Variables		Frequency	Percentage
APRI Score	APRI score < 0.7	31	36.9
	APRI score 0.7 to 1	14	16.7
	APRI score 1.01 to 2	17	20.2
	APRI score >2	12	14.3
	Not Available	10	11.9
HCV Genotype	Genotype 1	7	8.3
	Genotype 2	3	3.6
	Genotype 3	1	1.2
	Genotype 4	39	46.4
	Genotype 5	1	1.2
	Not available	33	39.3
Abdominal Ultrasound	Normal scan	39	46.4
	Portal hypertension with no cirrhosis	1	1.2
	Features of cirrhosis	34	40.5
	Only Splenomegaly	1	1.2
	Fatty liver	5	6.0
	Not documented	4	4.8

Treatment regimen and duration

The study found SOF/LED combination as the most commonly used regimen accounting for 50 (59.9 %) patients followed by SOF/DAC in 19 (22.6 %) and SOF/VEL in 10 (11.9 %). Majority (n=79, 94 %) were treated with a 12-week course regimen, 3 (3.6 %) patients with 24-week course regimen and Two patient were treated with 16 and 20-week course regimen.

DAA associated side effects were reported in 16 (19.1 %) patients, 15 (17.9 %) had fatigue and nausea where as one patient had headache.

Forty (47.6%) patients were taking concomitant medication while on DAAs, beta blockers and diuretics were the commonest followed by PPI, other antihypertensive agents, antidiabetic agents, statins, HAART, PTU, thyroxine and different anticoagulants.

Type of DAAs regimen used for treatment of chronic HCV infected patients is shown in Figure 1 below.

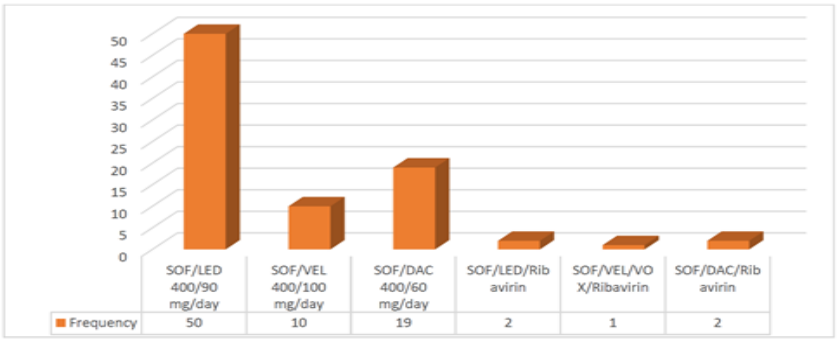

Figure 1: Types of DAA regimens used for treatment of chronic HCV infected patients treated at TASH and Adera specialty clinic from January 2018 and January 2020 G.C.

Treatment outcome

Viral load was determined 12 weeks after completion of therapy for all patients. Viral RNA was undetectable in 76 (90.5 %) patients and detectable in 8 (9.5 %) patients. SVR12 was achieved in 92.2% of treatment naïve and 71.5% of treatment experienced patients. Based on imaging findings, 93.5% of patients among those who have no liver cirrhosis and 85.3% of patients among those who have liver cirrhosis achieved SVR12.

Factors Affecting Treatment outcome

Since there is a low event rate of failed SVR (n=8, 90.5%), fisher's exact test was used to see for any association between the categorical independent variables and treatment outcome. Using this model, the degree of liver injury was found to have significant association with treatment outcome. None of the 31 patients with APRI Score of < 0.7 had treatment failure, while 7 of the 43 patients with APRI Score ≥ 0.7 had treatment failure with P value of 0.037.

No significant association was observed using other parameters like gender, presence or absence of liver cirrhosis based on imaging findings, previous treatment history, presence or absence of comorbidities, viral genotype, type of DAAs used and duration of therapy.

Fisher's Exact test of correlation showing the association between independent variables and treatment outcome of chronic HCV infected patients treated with DAAs is shown in Table 3 below.

Table 3: Fisher's Exact test of correlation showing the association between independent variables and treatment outcome of chronic HCV infected patients treated with DAAs at TASH and Adera specialty clinic from January 2018 and January 2020 G.C.

Factors		HCV RNA 12 weeks after completion of DAA				P Value
		Detectable		Undetectable		
		Frequency	Percent (%)	Frequency	Percent (%)	
Gender	Male	5	(13.6)	32	(86.4)	0.29
	Female	3	(6.3)	44	(93.7)	
Treatment Center	Adera	3	(6.6)	42	(93.4)	0.46
	TASH	5	(12.8)	34	(87.2)	
Comorbidity	Present	3	(9.3)	28	(90.7)	1.00
	Absent	5	(9.4)	48	(90.6)	
Previous HCV Treatment	Present	2	(28.5)	5	(71.5)	0.13
	Absent	6	(7.7)	71	(92.2)	
APRI Score	<0.7	0	(0)	31	(100)	0.037*
	≥ 0.7	7	(16.2)	36	(83.7)	
HCV Genotype	G-1	2	(28.6)	5	(71.4)	0.45
	G-2	0	(0)	3	(100)	
	G-3	0	(0)	1	(100)	
	G-4	4	(10.3)	35	(89.7)	

	G-5	0	(0)	1	(100)	
Liver status	Non cirrhotic	3	(6.5)	43	(93.5)	0.27
	Cirrhotic	5	(14.7)	29	(85.3)	
DAA Regimen	SOF/LED	4	(8.0)	46	(92)	0.19
	SOF/VEL	1	(10)	9	(90)	
	SOF/DAC	2	(10.5)	17	(89.5)	
	SOF/LED/ Ribavirin	0	(0)	2	(100)	
	SOF/DAC/ Ribavirin	1	(50)	1	(50)	
	SOF/VEL/VOX/ Ribavirin	0	(0)	1	(100)	
Duration of treatment	12 weeks	7	(8.9)	72	(91.1)	0.402
	16 weeks	0	(0)	1	(100)	
	20 weeks	0	(0)	1	(100)	
	24 weeks	1	(33.3)	2	(66.7)	

* Variables showing a significant association with detectable HCV RNA level at 12-weeks.

Discussion

In this study a total of 84 patients with chronic HCV infection were included. Mean age is 49±10.6 years and females accounted for 47 (56 %) cases. These numbers are comparable with previous studies from Egypt and Rwanda.

Among the 51(60.7%) patients with Documented chronic HCV infection, Genotype 4 accounted for 39 (76.5 %) patients followed by genotype 1 and 2. This result is in agreement with previous studies conducted in Ethiopia which reported similar finding of genotype 4 in 77.6 % of the study participants followed by genotype 2 and 1 respectively [4]. In another prospective study conducted in Ethiopia, genotype 4 accounted for 60% of the cases [3]. A recent prospective study done among Ethiopian chronic HCV infected patients also showed similar genotypic distribution [24].

Out of the 84 patients, 76 (90.5 %) achieved successful eradication of HCV. SVR was 93.5% among non-cirrhotic and 85.3 % among those who were diagnosed with cirrhosis based on imaging features (P value: 0.25). SVR12 was achieved in 92.2% of treatment naïve and 71.5% of treatment experienced patients but the difference was not statistically significant (P value: 0.13).

In this study, APRI score was used to assess the degree of liver fibrosis based on reports from previous studies [21]. There was a statistically significant difference in achieving SVR12 between patients with significant liver fibrosis (F2-F4) assessed by using APRI score cut point of 0.7. All of the patients with APRI score of < 0.7 achieved SVR while only 83.7% of the patients with APRI score of ≥0.7 achieved SVR (P- value: 0.037). There was no statistically significant difference in outcome using APRI score cut points of 1 and 2.

The result of this study is in accordance with other studies done in Africa. One study done in Rwanda on patients with Genotype 4 and 1 infection showed an overall SVR of 87%. The regimen used for this study was SOF/LED for 12 weeks. In this study, APRI score of ≥1 and genotype 4r were found to have significant association with non-response [23].

Another study done on patients of African origin using several combinations of DAAs showed an overall SVR rate of 89 %. In this study majority of the patients were infected with genotype 1 and 4. They reported that the use of NS5A based regimens and infection with unusual genotype 1 subtypes were found to have significant association with lack of SVR [25]. In our study there was no observed association between treatment outcome and the type of DAAs used as well as viral subtype patients had. However, there were few documented viral subtypes in our study and it is difficult to conclude. A Prospective study from Egypt using SOF/DCL and SOF/LED 12-week regimens, reported an overall SVR of 96 % and 98 % respectively. This outcome seems a little bit higher than our study but their study participants were only non-cirrhotic, treatment naïve genotype 4 infected patients [26].

A recently published prospective study conducted on 164 Ethiopian patients showed an overall SVR rate of

98.8%. In this study, 19% of patients had evidence of cirrhosis and SVR was 93.5% among cirrhotic and 100% among non-cirrhotic patients. Although the result of our study is almost comparable with this study, the slight difference in outcome could be due to difference in methodology [24]. The other possible explanations for lower SVR rate in our study could be due to higher number of patients with cirrhosis, differences in types of regimens used and duration of treatment.

In this study, we found out that patients who failed to achieve SVR had a higher baseline mean viral RNA level compared to patients who achieved SVR with P value of 0.66 which is close to the level of significance. Few studies reported association between higher viral RNA level and failure to achieve SVR. However, differences in SVR rates were observed between patients with higher and lower baseline viral RNA level [27].

With regard to the predictive factors associated with non-response to therapy, our result revealed that higher degree of liver fibrosis (F2-F4) assessed using APRI score is associated with failure to achieve SVR. Several studies have reported association of SVR rate with the degree of liver injury. Higher SVR rates were reported in patients with chronic hepatitis or child A liver cirrhosis than in those with child B or C liver cirrhosis [22, 23].

Conclusion

Based on this study majority of the patients were found to be infected with genotype 4 HCV. The most commonly used regimen was SOF/LED followed by SOF/DCL and SOF/VEL. These regimens appear to have favorable outcome with high rate of SVR and good safety profile in the treatment of chronic HCV infected patients. Presence of F2-F4 liver fibrosis assessed by using APRI score cut point of 0.7 was found to be associated with non-response to treatment.

Recommendation

We recommend to conduct a large multicenter prospective study in order to extensively look for predictors of outcome and degree of association including assessment of viral subtypes. We also recommend for the government, policy makers and the medical community to all work together towards further capacity building, diagnosis and treatment of chronic HCV infected patients in order to achieve the WHO goal of HCV elimination.

Strength and limitation of the study

The major strength of this study is being the first study to assess the efficacy of DAAs among patients having chronic HCV infection in Ethiopia and factors associated with it. Even though TASH and Adera specialty clinic are centers where patients are referred and managed from all over the country, majority of the patients (78.6%) in this study are from Addis Ababa. This might have an impact on the generalizability of the study. There are few numbers of patients with failed SVR which makes it difficult to assess the type and degree of association between some of the variables and the outcome. This is a retrospective study and there was incomplete data for some of the independent variables.

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Conflict of Interest

All authors declare there is no conflict of interest regarding this research.

Acronyms/abbreviation definition

AAU: Addis Ababa University
ADR: Adverse Drug reaction
ALT: Alanine Transaminase
AST: Aspartate Transaminase
CKD: Chronic kidney disease

DAAs: Direct Antiviral agents
DCV: Daclatasvir
DM: Diabetes mellitus
EGD: Esophago-gastroduodenoscopy
HBV: hepatitis B virus
HCC: Hepatocellular carcinoma
HCV: Hepatitis C virus
HIV: Human Immunodeficiency virus
HTN: Hypertension
IHD: Ischemic Heart disease
INF: Interferon
LDV: Ledipasvir
PT: Prothrombin time
SOF/LED: Sofosbuvir-Ledipasvir
SOF/DCL: Sofosbuvir-Daclatasvir
SOF/VEL: Sofosbuvir-Velpatasvir
SOF/VEL/VOX/Ribavirin: Sofosbuvir-Velpatasvir-Voxilaprevir-Ribavirin
SVR: sustained Virologic response.
TASH: Tikur Anbessa Specialized Hospital

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