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Treatment of Chronic Hepatitis C in Ethiopia: A Prospective Cohort study

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Abstract

Background: Direct acting antiviral treatment has changed the paradigm of hepatitis c treatment leading to high rate of sustained viral response. This study assessed treatment outcome of Ethiopian patients treated with direct acting antiviral treatment.

Objectives: The goal of this study was to describe the characteristics of patients with chronic hepatitis C and assess the Sustained Virologic Response (SVR) rate to the Direct Acting Antiviral (DAA) regimen.

Methods: This is a prospective cohort study, which has included eighty-seven consecutive patients treated with sofosbuvir plus Daclatasvir from August 2018 to July 2019. Data was analyzed by using statistical package for social sciences version 23. A Chi-square ($\chi 2$) test was used to test for the significance of association, p-value of less than 0.05 was considered as significant.

Results: From eighty-seven patients completed the treatment and follow up as per protocol, fifty-six (64.4%) were females, mean age was 48± 13. Fifty-two (59.8%) were non-cirrhotic, and thirty-five patients (40.5%) were cirrhotic. Genotype 4 was the most common genotype found in 46 (52.9%) patients. Overall sustained viral response as defined by undetectable viral RNA twelve weeks after completion of treatment is 80.5%, and evidence of cirrhosis on ultrasound, aspartate aminotransferase to platelet ratio index (APRI) score ≥ 2 and serum albumin <3.5g/dl were associated with treatment failure (defined by detectable viral RNA 12 weeks after completion of treatment). The mean baseline alanine transaminase and aspartate transaminases were 56.07 and 63.56 respectively and dropped to 25.04 and 30.9 twelve weeks after treatment completion.

Conclusion: Genotype 4 is the most common genotype and sustained viral response is lower than reported in clinical trial. There is improvement in liver transaminase with direct acting antiviral treatment.

Keywords: Viral hepatitis, DAA therapy, Sub-Saharan Africa, Epidemiology

Background

Hepatitis C infection is the leading cause of chronic liver disease including chronic hepatitis, cirrhosis and hepatocellular carcinoma. Globally, an estimated 71 million people have chronic hepatitis C virus (CHCV) infection (1). WHO estimated that in 2016, approximately 399,000 people died from hepatitis C, mostly from cirrhosis, end-stage liver disease and hepatocellular carcinoma (primary liver cancer) (Ref??). Currently there is no effective vaccine against hepatitis C. But there is a new oral direct-acting-agents (DAA) which has changed the treatment paradigm for HCV infection. Treatment of CHC with the currently available DAAs results in >90% sustained virologic response (SVR) which is equivalent to cure (2, 3). Achieving SVR after effective treatment with DAA halts progression of liver disease, decrease hepatic decompensation, need for liver transplant all cause and liver related mortality (4-6).Treatment of CHC improves work productivity and patient reported outcome (6-9). In this regard, treatment of CHC is cost effective.

However, DAA based regimen is not available in many low-income countries, because of countries or personal socio-economic status. The situation is worse in countries like Ethiopia, where there is no health insurance and citizens must pay out of pocket for diagnosis and treatment. In Ethiopia viral hepatitis is the most common cause of chronic liver disease (10), with 3.1% sero-prevalence, but the response to DAAs in Ethiopian Patients was not known. Hence, this study describes the characteristics of patients with HCV, assess the SVR rate to the DAA regimen, which is a surrogate marker for cure in Ethiopian patients who have follow up at a tertiary care.

Methods and Materials

Study setting, design, period, and population

The study is conducted at Saint Paul's Hospital Millennium Medical College which is in Swaziland Street of Gullele Sub-city in the northern part of the capital city of Ethiopia, Addis Ababa. For more information, visit (www.sphmmc.edu.et).

A prospective cohort study design was used. The study protocol was approved by the college IRB and informed written consent was obtained from each patient or guardian for those who couldn't give consent by themselves. The study was conducted from August 2018 to December 2019.

Sample size determination and data collection methods

Convenient sampling technique was used, and the first eighty-seven consecutive patients treated with DAAs were recruited. Patients with no evidence of cirrhosis were treated for 12 weeks and those patients with evidence of cirrhosis were treated for 24 weeks. And they were followed at 4 weeks, 12 weeks, 24 weeks, 36 weeks, and as routine thereafter. CBC, liver function test, renal function test, abdominal ultrasound, fasting blood sugar, HCV RNA (at baseline and SVR12), were performed and HCV genotype was determined by using Polymerase Chain Reaction (PCR) method. Patients under the age of 12, pregnant ladies, patients who develop HCC and patients who are unable to take oral medication were excluded from the study.

Data analysis and interpretations

Data analysis was performed by using the SPSS (statistical package for social sciences) version 23. The mean ± standard deviation (SD), median and ranges were calculated for continuous variables, whereas proportions and frequency tables were used to summarize categorical variables. A Chi-square ($\chi 2$) test was used to test for the significance of association between the independent (predictor) and dependent (outcome) variables for categorical variables. A p value < 0.05 was considered statistically significant.

Results

Patient characteristics

Eighty-seven patients were treated with Sofosbuvir (SOF) and Daclatasvir (DCV) from August 2018 to July 2019. Fifty-six (64.4%) of patients were females and the mean age of the patients was 48± 13. Fifty-two (59.8%) patients were non-cirrhotic, and thirty-five patients (40.5%) were cirrhotic based on criteria that comprises an ultrasound, Albumin <3.5 gm/dl, Platelet < 150,000 and Fibro scan > 10 KPa. Genotype 4 is found to be the most common type seen in 46 patients (52.9%) followed by genotype 1 twenty- three (26.9%) (See Table 1).

Table 1: Baseline characteristic of HCV patients treated with DAA regimen, Addis Ababa, Ethiopia (n = 87).

Variables		Frequency	Percentage
Age (in years)	Mean ± SD = 48± 13	87	100
Gender	Male	31	35.6
	Female	56	64.4
FBS	<126	68	78.2
	≥126	19	21.8
ALT	<2× ULN	69	70.3
	≥ 2× ULN	18	20.7
Serum albumin*	≥ 3.5g/dl	56	64.4
	<3.5g/dl	27	31
APRI score:	<2	72	82.8
	≥ 2	15	17.2
MELD score*	0-9	49	56.3
	10-15	28	32.2
	≥16	6	6.9
Liver status	cirrhotic	35	40.2
	Non-cirrhotic	52	59.8
Co-infection	HBV	2	2.3
	HIV	4	4.6
Rx experience	Naïve	85	97.7
	experienced	2	2.3
HCV VL (log 10 IU/ml)	Mean ± SD = 5.83 ± 0.87		
Genotype**	GT 1	23	26.4
	GT 2	8	9.2
	GT 4	46	52.9
	GT 5	1	1.1

**4 unknown; **9 undetermined ((undetermined Serum albumin was not done for 4 patients as a result MELD score was calculated for these patients. 9 patients were treated without determining the genotype); DAA- Direct acting antivirals, FBS-Fasting blood sugar, US-Ultrasound, GT-Genotype, ULN: Upper Limit of Normal*

Treatment Response

The SVR 12 of this study was 80.5% to the regimen given sofosbuvir (SOF) plus Daclatasvir (DCV). When we further do analysis based on their cirrhosis stage, the SVR in Non-cirrhosis was 88.5% and in cirrhotic individuals, it was lower at 68.6%. Treatment failure were associated with ultrasound evidence of cirrhosis, low serum albumin (<3.5 g/dl), and an APRI score ≥ 2 (See table 2).

Table 2: Variables associated with SVR 12 after antiviral treatment, Addis Ababa, Ethiopia (n = 87)

Characteristics		Overall N= 87	Patients with SVR	Patients without SVR	p-value
Serum albumin	≥ 3.5g/dl	56	49	7	
	<3.5g/dl	27	17	10	**0.009**
FBS	<126	68	57	11	0.134
	≥126	19	13	6	
APRI score	<2	72	61	11	**0.028**
	≥2	15	9	6	
US	non-cirrhotic	52	46	6	
	Cirrhotic	35	24	11	**0.022**
LSM	≤11.7	40	36	4	
	>11.7	43	33	10	0.103
Genotype	GT 1	23	17	6	0.822
	GT 2	8	7	1	
	GT 4	46	37	9	
	GT 5	1	1	0	
	Not determined	9	8	1	

** FBS: Fasting blood sugar, LSM: liver stiffness measurement, SVR: sustained virologic response, US: ultrasound*

Biochemical response

The mean AST was dropped from 63.56 at baseline to 30.9 and the mean ALT dropped from 56.07 at baseline to 25.04 at 12 weeks post-treatment follow-up. There is improvement in AST and ALT in both who achieved SVR12 and who don't achieve SVR12, but the mean AST and ALT is lower in those who achieved SVR12.

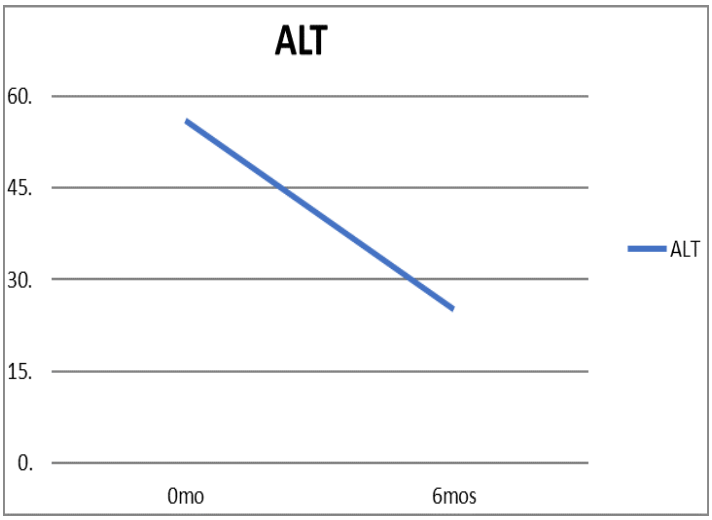

Figure: ALT improvement in CHC patients treated with DAAs

Discussions

This is a study which was done in one of the major referral liver clinics in Ethiopia. The findings have shown that treatment is effective, and patients have shown marked improvement irrespective of the stage of their liver disease. We have collected data from patients who were being treated in the hospital and at the clinic, patients were taking the available drug, Daclatasvir/Sofosbuvir, as a pan-genotypic treatment regimen. The virologic response in patients who have cirrhosis was lower, but still showing a benefit, as these patients would have been following the natural course of the disease, if treatment was not provided. We have shown the prevalent genotype of the virus, failure rate to DAA regimen and the importance of early treatment in relation to cure.

Most of the patients (97.7%) are treatment naïve, and genotype 4 is the most common genotype identified in 46 patients (52.9%) which is comparable to previous studies done in Ethiopia (11, 12).

The mean age of patients was 48 years which is comparable with a population-based study from Rwanda reported mean age as 44.8 years. The same study has also reported that 65 years and older (OR = 4.86, 95% CI: 4.62–5.11) was significantly associated with HCV infection (13). The identified mean age with standard deviation indicates the appropriate

target age groups for HCV screening in Ethiopia. Based on fibrosis markers, thirty-five (40.2%) were having cirrhosis. This is a higher number that warrants strengthening policy makers to advocate screening mechanisms to diagnose patients at the earliest stage possible.

The treatment efficacy can be determined using different surrogate markers. One of the widely used markers is assessing the Sustained Virological Response at 12 weeks of completion of therapy (SVR 12), which is equivalent to cure. Overall SVR12 was found to be 80.5% which is lower than clinical trials report >90% (14, 15) and when we divide this outcome based on cirrhosis; 88.5% in non-cirrhotic individuals and 68.6% in cirrhotic. The SVR 12 has been lower in ALLY-1 trial, where the SVR-12 was 56% in patients with Child-Pugh C, while 92-94% in B and A respectively (16), showing that advanced cirrhosis associated with worse outcome. The WHO Guideline has recommended Daclatasvir/Sofosbuvir for Genotype 1, 3 and 4 without cirrhosis and 1 and 4 with cirrhosis (17). Egypt has used the same regimen as a pan-genotypic for more than a million patients and both countries share predominant genotype 4 followed by 1 (18). The Ethiopian National Guideline on Viral Hepatitis treatment also recommends using Daclatasvir/ Sofosbuvir as a first line pan-genotypic drug (19). Nevertheless, the decreased efficacy from different literatures is due to provision of the drugs in advanced cirrhosis and treatment experienced individuals. The study drug hasn't shown any side-effects and no patient has discontinued the drug due to adverse events in this study. The lower SVR in this study also alarms concern, which has been raised by Neil et al in a correspondence published at the Journal of Hepatology, which questioned the first line antivirals used in Sub-Saharan Africa (20).

There was improvement in liver transaminases which was seen in both who achieved SVR12 and not achieved SVR. But the decrement was higher in those who achieved SVR12. Similar finding was also reported in a study done in Egypt (16). As ALT has been considered as a marker of inflammation normalization of ALT with a mean level of 25 mg/dl after one year of treatment is a vital marker of improvement and associated with less progression to fibrosis and cirrhosis and hence to HCC.

Conclusion

Hepatitis C Virus treatment in Ethiopia has shown improvement in signs of liver inflammation based on laboratory tests and SVR 12 rates. The improvement was marked in those without cirrhosis and however, it was lower in patients with cirrhosis and compared to studies from other comparative studies. Therefore, earlier identification of HCV infection, linkage to care and timely initiation of anti-viral treatment - prior to the development of cirrhosis and decompensation, which could be irreversible - is highly required to reach the WHO goal of eliminating viral hepatitis as a public health treat by 2030. This study can provide a valuable information on the efficacy of DAA regimen in different levels of liver fibrosis and varied genotypes for other African countries aiming to scale up treatment of Hepatitis C Virus infection.

Abbreviations

ALT: alanine aminotransferase; APRI: aspartate aminotransferase to platelet ratio index; AST: aspartate aminotransferase; CHC: chronic hepatitis C; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; SVR: Sustained Virological response; WHO: World Health Organization

Declarations

Ethics approval and consent to participate

The study was approved by Institutional Review Board (IRB) at St. Paul's Hospital Millennium Medical College (SPHMMC). Informed written consent was obtained from all study participants or their guardians for those patients who couldn't give written consent before enrolment to the study. In those participants who are aged between 12 to 18 years, consent was obtained from adult family member or care giver. Patients were told that their participation is voluntary, and the right to withdraw at any point if they wanted to. They were also informed about the absence of negative consequence of not participating in the study, they were reassured that the usual care will be continued. In addition, participants were also told that the information gathered will only be used for the study purpose.

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Competing interest

All the authors read and agreed on the final manuscript and also declare that they have no competing interests.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions

HD: was involved starting from proposal writing, getting IRB approval, patient management and follow up, data analysis and manuscript writing. YC: contributed to draft proposal writing, literature review, patient management and follow up, data clearance and analysis, manuscript writing and submission. PS and MD: were involved in literature review, data collection. HA: was involved in data collection

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