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ORIGINAL ARTICLE

COMMON GENOTYPES AND TREATMENT OUTCOMES OF HCV INFECTION AMONG ETHIOPIAN PATIENTS: A PROSPECTIVE STUDY

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ABSTRACT

Background*: The treatment response of HCV infection is dependent on genotype and stage of the disease. However, genotype pattern and treatment outcomes of HCV infection among Ethiopian patients has not been studied so far.*

Objectives*: To evaluate the common HCV genotypes and treatment outcomes among Ethiopian adult patients.*

Method*: Adult patients aged 18 and above with HCV infection referred from various regions of the country were included in the study after written informed consent. As there was no free or insurance coverage for treatment of HCV infection in the country, those who could afford to pay for treatment with PEG Interferon and Ribavirin were recruited during January 1, 2008 through December 31,2013 at United Vision, Adera, Old Airport, and Mexico referral higher clinics in Addis Ababa. Patients with decompensated cirrhosis and pregnant ladies were excluded from the study. The patients were counseled on treatment options, cost, treatment outcomes, adverse drug effects, and possible complications. Data were collected on demographic features, clinical characteristics, viral genotypes, and treatment outcomes during follow up visits until six months after completion of recommended standard treatment. Data were analyzed using SPSS software.*

Results*: A total of 200 adults with chronic HCV infection were treated with PEG -Interferon and Ribavirin (for 24 or 48 weeks according to the genotypes) during the study period. Of the 200 patients enrolled in the study, 120 (60%) were male, 90% were from Addis Ababa, and the median age was 48 years. Sixty per cent of the patients were infected with genotype 4,17% with genotype 1, 13.5% with genotype 2 and 9.5% with genotype 3.*

Eighty percent of the patients had end of treatment response; of these, 74.4% had undetectable HCV RNA at6th month after end of treatment. The end of treatment response was noted to be close to 90% for patients with HCV genotypes 2 and 3 infections.

Conclusion*: This study indicates that genotype 4 is the prevalent HCV genotype followed by 1,2, and 3 among Ethiopian patients. Treatment with interferon and ribavirin was well tolerated and provided a very good response.*

Key words*: HCV, genotypes, treatment, Ethiopia.*

INTRODUCTION

Hepatitis C virus (HCV), a single stranded ribonucleic acid virus belonging to the flaviviridae family, is one of the major global health issues affecting humans.(1) It is most often transmitted parenterally but is also transmitted vertically and sexually. HCV is up to 4 times more infectious than Human Immunodeficiency Virus (HIV).(1) HCV is classified on the basis of the similarity of nucleotide sequence into major genetic groups designated genotypes. HCV genotypes are numbered (arabic numerals) in the order of their discovery. The more closely related HCV strains within some types are designated subtypes, which are assigned lowercase letters (in alphabetic order) in the order of their discovery. The complex of genetic variants found within an individual isolate is termed the quasispecies. The quasispecies composition of HCV results from the accumulation of mutations during viral replication in the host. (1-3)

The World Health Organization (WHO) estimates that HCV infection causes 54,000 deaths and 955,000 disability adjusted life-years worldwide annually.(2) Recent estimates show an increase in sero prevalence over the last 15 years to 2.8%, equating to greater than 185 million HCV infections globally.(3)

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HCV is also a common cause of death in HIV-positive patients on highly active antiretroviral therapy.(4,5) While the incidence rate of HCV infection is apparently decreasing in the developed world, deaths from HCV-induced liver diseases are estimated to rise over the next years from related complications like cirrhosis and hepatocellular carcinoma (HCC).(4,5-12)

HCV pandemic is a leading cause of chronic liver disease worldwide. The prevalence of HCV in the general population in Africa ranges between 0.1% and 17.5%, depending on the country reporting. The countries with the highest prevalence include Egypt (17.5%), Cameroon (13.8%) and Burundi (11.3%) while lowest prevalence was reported from Zambia, Kenya, Malawi, and South Africa (all with a prevalence <1%).(6-13, 20, 21)

Since there is no effective vaccine yet, primary prevention against hepatitis C focuses on reducing risks of infection through educating people on safe sex, safe protocols while using needles and syringes, and blood safety. Very effective directly acting antiviral treatment is now available to treat HCV infections. HCV is curable with this effective therapy in 60-98% of cases. Although we have an effective therapy for hepatitis C, lack of knowledge and skill to deliver treatment among providers, and the high cost of HCV genotyping and drugs, make access to treatment a major global limiting problem yet.(6-13)

Viral hepatitis is noted to be endemic in Ethiopia accounting for significant morbidity and mortality. (14) According to a United Nations report from 2000, HCV seroprevalence in Ethiopia, based on five cohort studies with a sample size of 2,080 tests, was estimated to be 1.9%.(15) In another study among HIV co-infected patients, sero-prevalence was 5.5%. (16-17) There were no treatment options available for HCV infection in Ethiopia until recently. No study has therefore been carried out to identify HCV genotypes and compare treatment response in Ethiopia yet. Hence, we studied the prevalent genotypes and treatment response of HCV infection among Ethiopian patients.

METHOD AND MATERIALS

This is a prospective clinical treatment follow up study. The study protocol was reviewed and approved by the Institutional Review Board of the School of Medicine at Addis Ababa University. Adult patients (aged 18 years and above) with HCV infection who were referred from various regions of the country for specialty care, were evaluated for treatment. Confirmatory tests were done using the ARCHITECT i2000SR automated analyzer from Abbott Laboratories (USA) for those who had positive anti HCV rapid tests. Then, sera of those with confirmed HCV infection were sent abroad for HCV viral load and genotype determination using TaqManreal time reverse transcriptase PCR at Bioscientia GmBH in Germany, as these tests are not available in Ethiopia to date. Those patients with confirmed HCV infection and compensated liver disease, who could afford the treatment cost with PEG interferon and Ribavirin (the only treatment option available for HCV in the country during the study period), were recruited into the study after written informed consent.

Those with decompensated cirrhosis and pregnant ladies were excluded as interferon is contraindicated in these conditions. The recruited patients were treated and followed up prospectively every 2-4 weeks (for clinical response and adverse drug side effect) by senior Gastroenterologists at United Vision, Adera, Old Airport, and Mexico referral higher clinics in Addis Ababa during January 1, 2008 through December 31, 2013. The patients were counseled on the available treatment options, cost of care, treatment outcomes, drug adverse effects, and possible complications.

The patients were treated and dose adjustments were made for minor adverse effects (like pancytopenia, anemia, etc.) during follow up by the treating Gastroenterologists. During each follow up, data were collected on demographic features, clinical characteristics, adverse drug reactions, and treatment response of the patients. Viral load was measured at base line, 12 weeks,24 weeks and48 weeks after initiation of treatment, as well as 24 weeks after completion of treatment Despite the treatable minor adverse effects, all the patients completed the treatment schedule (24 or 48 weeks for genotypes 2 and 3; 1 and4 respectively) and were included in the data analysis. The data were analyzed using SPSS software.

RESULTS

A total of 200 adults with chronic HCV infection were included in the study and treated with PEG Interferon and Ribavirin during the study period. Of the 200 patients enrolled in the study, 120(60%) were

male and 90% were from Addis Ababa, with median age of 48 years. There were 91 patients treated at United Vision higher clinic, 63 at Adera higher clinic, 37 at Old Airport higher clinic, and 9 at Mexico higher clinic. The majority (90%) of the patients were married. (Table1) History of jaundice, liver disease in family, previous surgery was reported by 11.4%, 32.6%,and 7.8% of the patients, respectively. Fifty-nine(30.6%) patients admitted history of regular alcohol consumption while only 1 patient admitted a history of IV drug use.

As shown in Table 2 one hundred twenty (60%) of the patients were infected with genotype 4 HCV followed by genotypes 1,2 and 3 in decreasing order while seven patients had mixed genotypes 1 and 4. (Fig.1) In this study, types a, b, c, d, e were the common HCV subtypes reported. Afew others could not be classified. As multiple HCV subtypes were reported for each patient, the percentage of HCV subtypes does not add up to 100 as shown in Fig 2.

Table 1. Socio-demographic characteristics of patients with HCV infection, Addis Ababa 2014.

Variables	Number	Percent
Health institutions		
UVC	91	45.5
AHC	63	31.5
MHC	9	4.5
OAHC	37	18.5
Total	200	
Sex of the respondents		
Male	118	59.0
Female	82	41.0
Total	200	
Age group of the patients		
<35	29	13.6
35-44	44	22.2
45-54	60	30.3
55-64	55	27.8
65 and above	12	6.1
Total	200	
Mean	48.33	
+SD	12.16	
Marital status		
Single	15	7.5
Married	180	90.0
Divorced	2	1.0
Widowed	3	1.5
Total	200	
Occupation		
Civil servant	92	48.9
Merchant	34	18.1
House wife	48	25.5
Other	14	7.4
Total	188	
Address		
Addis Ababa	181	90.5
Out of Addis	19	9.5
Total	193	

Table.2 HCV genotypes and treatment response, Addis Ababa, 2014

Genotype	Number (% total study participants)	End of treatment response Number (% of those with genotype)	Sustained Viral response Number (%of those with genotype)
1	34 (17.0)	23(68.5)	18(53)
2	27 (13.5)	24 (90)	23(85)
3	19 (9.5)	17(88)	14(80)
4	120 (60)	91 (75.7)	58(64)

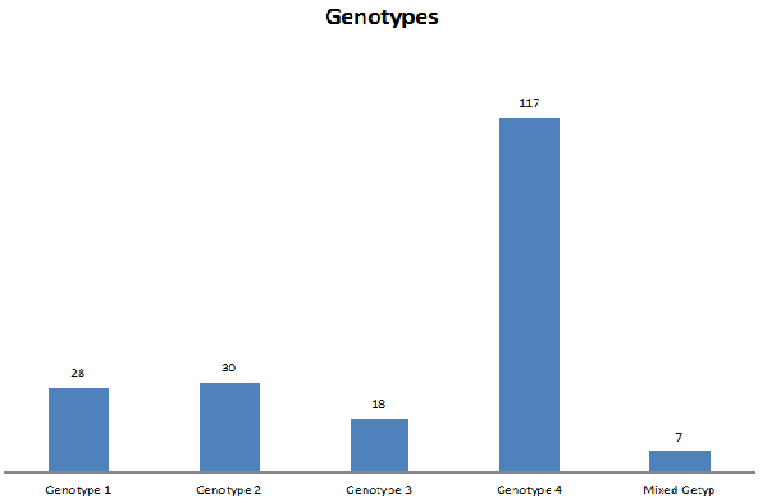

Fig 1. Number of patients infected with specific HCV genotype, Addis Ababa

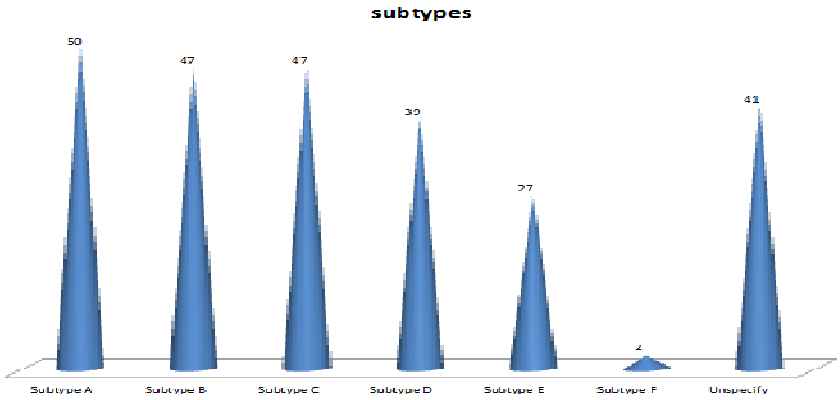

Fig. 2. Number of patients infected with HCV Sub types, Addis Ababa, 2014

Fifty percent of the patients reported minor side effects like fatigue, insomnia, hair loss, anemia, and flu like symptoms but all of them could complete the treatment course without interruption and responded to symptomatic treatment (and drug dose adjustment) for the adverse effects.

Overall, eighty percent of the patients had end of treatment response of whom 74.4% had undetectable HCV RNA at 6 months after end of treatment (sustained virological response, SVR). SVR was noted to be higher for genotypes 2 and 3 compared to others as depicted in table 2.

DISCUSSION

HCV exhibits high genetic diversity, characterized by regional variations in genotype prevalence. This has been the challenge to development of vaccines and pan-genotypic treatments[18]. There are six major HCV genotypes with many subtypes: a, b, c, and about 100 different strains: 1,2,3--- based on the sequence of the HCV genome. Genotypes 1-3 are widely distributed globally (more in the west), with genotypes 1a and 1b accounting for 60% of infections worldwide. Genotype 4 is characteristic for the Middle East, Egypt and Central Africa. Genotype 5 is almost exclusively found in South Africa while genotype 6 is mainly distributed in Asia(1,10,18-22)

In this study, four different genotypes were identified among Ethiopian patients, 60% being genotype 4,17% genotype 1, 13.5% genotype 2 and 9.5% genotype 3(Table 2), which is similar to reports from the Middle East, North and Central Africa possibly suggesting the routes of its global spread following human migration and travels [20].Subtypes a, b, c, d, and e were the common subtypes reported. Mixed genotypes and unclassifiable HCV subtypes were noted inonly very few of our patients. As deduced from multi centre epidemiological studies, the routes of HCV transmission include blood, blood products, tissue and organs; unsafe medical procedures; healthcare exposure like needle stick injury; intravenous drug use; sexual transmission; traditional body piercings, and vertical transmission, which is higher with HIV coinfection(1,2,20,21). Although difficult to confirm from our own data due to study design limitations, similar risk factors as reported elsewhere could have contributed to HCV infection among our patients; but this needs a further case control study.

According to international guidelines, all patients with chronic hepatitis C infection should be considered potential candidates for drug therapy. Treatment is recommended for patients who are at risk of developing cirrhosis, generally defined by a measurable hepatitis C RNA level and liver biopsy or fibroscan showing portal or bridging fibrosis along with moderate inflammation and necrosis.[20-21]In our case, decision to treat our patients was based on clinical evaluation, A separate aminotransferase (AST) to platelet ratio index (APRI,) scores, liver chemistry, and abdominal sonography results. Accordingly, all patients with chronic hepatitis C and compensated cirrhosis were given treatment and followed up for treatment response and drug adverse effect monitoring using the same parameters. However, Fibroscan/ Elastography liver stiffness test was not available in Ethiopia during the study period and was thus not used. As it is invasive, liver biopsy is also optional and according to our own observation, most patients are against it.

The treatment goal in HCV is to achieve a sustained virological response (SVR), defined by the continued absence of hepatitis C RNA from the treated patient6 months after the completion of treatment. (20-24) Treatment for chronic HCV infection has evolved from interferon monotherapy, which results in an SVR of 10 to 20% to combination therapy with interferon plus ribavirin, and recently with new directly acting antiviral drugs (DAAs) which results in a higher SVR rate (but not yet available in Ethiopia) (20-21).

Genetic heterogeneity of HCV may account for some of the differences in disease outcome and treatment response observed in patients infected with HCV. (25)Treatment duration and response of HCV is also dependent on the viral genotype. Hence, identifying the common genotypes and subtypes prevailing in the country is essential for planning and selection of treatment. According to our finding, genotypes 4,1,2 and 3 are the predominant genotypes in Ethiopia. Similar to international experiences, our patients with HCV genotypes 4 and 1were relatively difficult to treat and required a longer (48 weeks) treatment duration with PEG Interferon-Ribavirin combination. The response to treatment was lowest in patients with genotypes 1 and 4 among our series. Since these make up a large percentage of our cases (almost three -fourths in our study), there is a strong need for alternative treatment for HCV in Ethiopia.

However, genotypes 2 and 3 were easier to treat and higher SVR could be achieved with shorter treatment

duration (24 weeks). The overall SVR and treatment tolerance in this study is very good and comparable to many other regional and international studies(4, 6,20-24) Most patients tolerated the medications, despite minor side effects, with very good response having SVR of 85%, 80%, 64%and 53% in genotypes 2,3,4, and 1 (with overall SVR of 74.4%). Hence, with availability of HCV genotype data and effective therapies, physicians, researchers, and health care decision makers need to improve efforts to promote the capacity of diagnosis, management, and prevention of HCV in Ethiopia.

Conclusion*:* From this study, HCV genotype 4 is the most prevalent among Ethiopian patients followed by genotypes 1,2 and 3 in decreasing order. The treatment with PEG Interferon and ribavirin was well tolerated by the patients with very good outcomes. Hence, a concerted national effort is needed to promote awareness and build diagnostic and treatment capacity within the country as well as to establish screening and preventive programs to overcome the current challenges of endemic HCV infection in Ethiopia, a disease which is associated with significant morbidity and mortality and leads to huge health service costs.

Limitation of the study: Not all adult patients with HCV infection who deserve treatment were included in this study due to financial constraints. Patients with decompensated cirrhosis and pregnant ladies were also excluded from this study as interferon is contraindicated. These exclusions might have biased the outcomes of our study and limited extrapolations.

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