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Original Article

Association of HCV Load and Interferon Therapeutic Response with Gender in Hepatitis C Patients Presenting to a Tertiary Care Health Facility, Rawalpindi

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Abstract

Background: This Study was conducted to compare mean levels of quantitative PCR (RNA) of males and female Hepatitis C positive patients along with any disparity in responsiveness towards interferon therapy between males and females.

Methods: This cross sectional analytical study was conducted from February 2015 to January 2016 at the Liver Centre of Holy Family Hospital, Rawalpindi, Pakistan. 204 patients of Hepatitis C, 104 males and 100 females were selected through Simple Random Sampling. The data was collected from the records of the patients regarding gender, HCV load, Quantitative PCR (polymerase chain reaction) to interferon, past surgical and transfusion history.

Results: Mean PCR of females was 4.57E6± 1.998E7 IU whereas mean PCR of males was 3.04E6 ±8296048.199 and this difference was not statistically significant, (p=0.47). Among the males, 46.26% did not respond to the interferon treatment whereas those who responded were 34.69%. While among the females, 65.30% of did not respond to treatment and 34.70% responded, with a statistically insignificant difference (p=0.2).

Conclusion: HCV load is unequivocally distributed amongst males and females. Females emerged as better responders to conventional pegylated 2 alpha interferon therapy than males.

Key Words: HCV, viral load, interferon, response, gender, Polymerase Chain Reaction.

Introduction

HCV load corresponds to the number of virus particles circulating in the blood serum. HCV load depends on being exposed to and then harbouring the HCV inside the body. It is not mere getting the virus inside your blood rather to have it nurturing in the serum due to inability to ward it off from the body. Poignancy for having HCV retained within the body correlates with sustainability of virus. The sustainable survival of HCV is related to non-responsiveness or reduced response to therapy, and presence or absence of certain inherent inhibitors of virus induced damage. HCV load thereby is born via reduced treatment response and dis-inhibition of viral replication and virus provoked damage, once HCV has penetrated the barriers. HCV load distribution between males and females attracts curious researches. HCV load is precariously heavier in men than in women whilst females emerging as better interferon responders.

Gender has been rendered a milestone in defining innate tendency to eradicate HCV; the spontaneity with which females abate the HCV load is higher than in males. [1,2] Premenopausal females are better candidates for interferon responsiveness owing to their lower BMI than men and young age thereby, many women are spared of HCV load despite getting infected.[3,4] Nevertheless, there is inevitability in the fact that female sex hormones facilitate responsiveness to interferon. [5,6] Vindictively or naturally testosterone promote expression of scavenger receptors found on human monocyte-derived macrophages and HepG2 cell, receptors on which HCV binds resulting in harbouring higher HCV loads in males than females. [7,8.]The inhibitory action of 17β-estradiol on release of mature virions observed in Huh-7.5 cells transfected with viral replicon in culture make females better candidates for responding to interferon, for interferon also interferes with viral replication. [9] Progesterone ceases to produce same inhibitory impact in the similar culture. [9] Chronic HCV activities are found to be reduced in pregnancy predilection somewhat bias of HCV in favour of females by sparing them. [10] In contrary to previous researches, Watashi et al. reported HCV replication is correlated with oestrogen receptor-α activity, making females more vulnerable for harbouring HCV loads.[11]

The available literature on the correlation of gender with HCV load was negligible in Pakistan while with that of interferon response was scanty. This study can lead to an interesting probe in Pakistan, where previous International researches are not conclusive on

a single point and develop contradictory inferences regarding HCV load with gender. The antagonism observed in different research studies procrastinate ambiguity regarding gender bias which some researches hold with HCV load for many infer that males are more prone to retain higher HCV loads than females. Some propose gender bias for HCV load to response to therapies and others base it on inherent defence in female gender. The correlation of gender with HCV load has vital role to play in determining effective therapeutic approach in different genders apart from entirely divergent prognostic interventions. While studies label females as better interferon responders, our study will try to predict the righteous gender for interferon therapy conventionally while giving novice therapeutic approach to the gender lagging behind in interferon response. This could also make one of the genders once exposed to HCV as more preferred subject of early interventions and investigations to prevent advanced HCV complications like cirrhosis and HCC.

The objective of our study was to compare the mean levels of quantitative PCR (RNA) of males and female Hepatitis C positive patients and also to compare responsiveness towards interferon therapy between males and females presenting to Liver Centre, Holy Family Hospital Rawalpindi.

Alternate hypothesis of our study were

i) Mean levels of quantitative PCR (RNA) levels are not the same in male and female Hepatitis C patients.
ii) Females are better responders to interferon therapy.

Materials and methods

This cross sectional analytical study was conducted at Liver Centre of Holy Family Hospital, Rawalpindi, Pakistan. Study population comprised of chronic Hepatitis C patients with confirmed diagnosis, admitted in Liver Centre of Holy Family Hospital, Rawalpindi from February 2015 to January 2016. According to reference values given in parent study with power of test 80% and level of significance 5 %, the minimally required sample size for our study was calculated to be 204 with 102 males and 102 females. [12]

From all the registered patients at the Liver Centre, Simple Random Sampling technique was applied, using SPSS generated random number list. All the relevant information from the records of the selected patients was deduced after their verbal informed consent and was recorded in the structured checklists formulated for this study. All the information regarding, gender, HCV load (qualitative PCR assay), interferon conventional therapeutic response of patients, past surgical history and blood transfusion history was collected. Viral load corresponds to the amount of the viruses one has flowing in his blood in a specific volume (usually 1millimeter=1cubic centimetre). The amount of hepatitis C genetic substance found in the blood refers to number of viruses circulating in the blood. It can also be perceived as viral equivalents.

Quantitative HCV loads are the figures of the measured HCV viruses in the blood. Following reference ranges for ascending HCV loads were used in the study:

Low 200,000 to 1,000,000 IU/L
Medium 1,000000 to 5,000,000 IU/L
High 5,000,000 to 25,000,000 IU/L
Very high above 25,000,000 IU/L

Pegylated interferon alfa – 2a is an antiviral drug, which has a longer half-life than innate human and native interferon via its pegylation. All Patients included had confirmed diagnosis of chronic liver disease by anti-HCV core antibodies and chronicity of disease with development of complications like ascites, cirrhosis etc. All patients were having conventional therapy with interferon or had treatments with it. All patients with confirmed history and diagnosis of IV drug abuse, pregnancy and AIDS were excluded.

Data entry & analysis was done in SPSS (Statistical Package of Social Science) version 22. For numerical variables like age and quantitative PCR RNA levels mean, mode, range and standard deviation were calculated. To compare the mean levels of quantitative PCR (RNA) or viral load of male and female patients' independent samples "t" test was applied at 5% level of significance. For categorical variables like gender, categories of viral load and responsiveness to interferon therapy, frequencies and percentages were calculated and Pearson's Chi square test was applied to compare the categories of viral load and responsiveness in both male and female patients. A p value of < 0.05 was considered statistically significant.

Results

Based on completion of available samples, 104 males and 100 females were included in study. Total respondents were 204 which had mean age of 48.33 years ±11.162 years where median and mode of age were 50 years each. Youngest patient was 13 years old where the eldest was 80 years old with range 67 years. Mean age of females was 48.89 years±11.648 years whereas mean age of males was 47.73yrs ±11.53 yrs.

Mean Quantitative PCR of all 204 patients was 3.79E6 ±1.517E7 IU (International units) where median was 6.98E5 IU while mode was 30E3 IU. Minimum PCR value was 30 IU whereas highest value was 2E8 IU with range of 2.0E8 IU.

Mean PCR of females was 4.57E6 ±1.998E7 IU where mean PCR of males was 3.04E6 ±8296048.199 IU and this difference was not statistically significant with a t-value of 0.71 and p value of 0.473 upon applying independent sample's t test. Overall 17.2% of patients amongst all 204 had high, 24.5% had medium, 31.4% had low and 27% had very low viral loads. When these were compared based on gender, no statistically significant difference was observed amongst male and female patients with a chi value of 1.01 and p value of 0.797. Difference is shown in Figure I exhibiting categories of viral loads in male and female patients.

Amongst 204 patients, 48 (23.52%) patients did not respond to previous interferon therapy while 68 (33.33%) did respond, shown in (Table I). When gender wise comparison was made between responders and non-responders (excluding naive and partial responders), amongst 67 males, 31 (46.26%) did not respond to the interferon treatment whereas 36 (53.74%) did respond. Out of 49 female patients, 17(34.70%) did not respond to treatment while 32(65.30%) did respond to it, though this difference was not statistically significant with a chi value of 1.52 and a p value of 0.2.

Table-I Comparison of Treatment Response Of Interferon Therapy

GENDER	NAÏVE *f (%)	NON RESPONDER	PARTIAL RESPONDER	RESPONDER	TOTAL
MALES	34 (32.69%)	31(29.80%)	3 (2.89%)	36 (34.62%)	104 (100%)
FEMALES	51 (51.00%)	17 (17.00%)	0 (0.00%)	32 (32.00%)	100 (100%)
TOTAL	85 (41.66%)	48 (23.53%)	3 (1.48%)	68 (33.33%)	204 (100%)

*f (%)= frequencies (percentages)

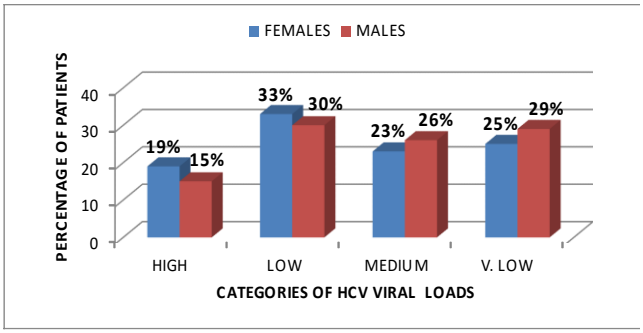

Figure I. Comparison Of Hcv Viral Load Based On Gender

Out of 204 chronically ill HCV patients, only 42 (20.6%) had positive history of blood transfusion while 162 (79.4%) having a negative history for the variable. Whereupon the gender of the chronically ill HCV patients was considered, blood transfusion history was positive in 29% females as compared to 13% of males, giving a difference to gender predilection of HCV in terms of blood transfusion kept as a sacred risk factor. Upon applying the Chi Square test the difference was highly statistically significant with a p value of 0.00. Whereupon in aspect of other risk factor of past surgical history, 54% HCV loaded females had a positive history in combat with 35% males positive for HCV with highly statistically significant difference having chi value of 7.7 and the p value of .005.

Discussion

In our parent study from Guangzhou , China in 2001 to 2009,[12] one of the significant association found in previous studies was refuted giving the bias towards the gender probed over in other studies as non-existent. According to our study, HCV load is indiscriminately distributed amongst both genders. Our findings are inconsistent with the internationally commented results in various foreign studies. Moreover the interferon drug responsiveness was commented as higher in females than males which was consistent with the international studies' results.

In the reference study, having .006 as 'p' value, HCV loads among males were higher than females about 2.5 times. Of the total population 71.1 % of the HCV patients having significant viremia were male population in the study while only 28.9% of the HCV loaded patients were females. Contrarily, in our study group of 204, about 51% were males while 49% were females giving no statistical significance upon applying Chi Square test with a 'p' value of 0.797.

A study conducted at Ayub Medical College , Abbottabad in 2014 [13], response to interferon was found to be higher in males i.e., 76.14% compared to that with females, i.e., 72.77%, while partial response was almost same in both the sexes (88.71% in males and 89.93% in females). However, our study had contrary results where females emerged as better responders with 65.30% females were responders compared to 53.73% responding males . Our study contrasted in terms of interferon response with this study [13] establishing females as better responders to conventional interferon in chronic HCV illness, though results are not statistically significant.

In a study conducted on 100 chronic HCV patients [14], with 50 males and 50 females, rate of therapeutic

response to conventional interferon was significantly higher in women than in men (66.7% vs. 38.2%, P < 0.05) giving a P value of 0.001 which supported our calculations. Hence, giving the same results with females emerging as better interferon responders.

In a study conducted at a liver centre in Italy [5], 41 out of 55 males (74.55%) exhibited virological response to interferon while 156 out of 172 females (90.6%) were responsive to interferon therapy with statistical significance in responsiveness between males and females according to a 'p' value of 0.006. Our study exhibited consistency in term of results, though the rates of responsiveness in both males and females are not that much higher. In our study at Holy Family Hospital Liver Centre about 34.70% females were non responders while 53.73% males were non responders in contrast to 25.55% non-responder males and 9.4% non-responder females in the study [5]. Our study thereby held similarity with the study mentioned, with lesser females with failure to respond as compared to males.[5]

The strength of our study is that it encompasses interferon, the most widely used conventional therapy, effectiveness in different genders of patients who have developed complications of chronic HCV infection apart from screening the prone gender to complications which is a sui generis and pioneer study, in this regard, in our set up. It instigates new researches in this dimension to be undertaken by our country specialists. Whereas the frailty it holds is that it does not encompass the combined drug regimens with interferon effectiveness in different genders as well as it does not classifies the female population into premenopausal and postmenopausal , and pregnant and non-pregnant categories while evaluating the gender bias of HCV load distribution and interferon responsiveness . Even though the difference in treatment is in consistency with the previous researches, our methodology did not follow up each patients after initiation of treatment and measured the responses of treatments once the patients had completed the treatment, hence missing the information relevant to compliance of patients with the treatment and the severity of illness or concurrent complications of the disease during treatment period that might have affected the outcomes.

HCV patients should be subjected to high surveillance to prevent development of complications irrespective of any gender bias for many studies claim males to be at high risk for acquiring higher HCV load. Risk factors should be surveyed as well and as our study claims that blood transfusion is a higher contributing factor in females when it comes to harbouring a significant HCV load, thereby females having undergone blood transfusion and surgeries must be monitored more often for HCV development and its complications like cirrhosis and HCC. Moreover HCV loaded males should be given longer follow ups and more effective drug regimens once their interferon therapies are initiated as, according to our study, females respond better to interferon. Hence gender is not biased when it comes to HCV load, it has equal discrepancies but some risk factors as transfusion and past surgical history make females slightly at a higher risk of being HCV loaded than males but males lag behind in therapeutic response.

Conclusion

Gender did not pose a core value in determining HCV loads. The distribution of HCV loads amongst various viral load groups were gender independent. Females emerged as better responders to conventional pegylated 2 alpha interferon therapy than males.

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References

1. Fedorchenko SV, Martynovich TL, Liashok OV, Kariuk ZhA, Ianchenko VI. Spontaneous HCV clearance: an association with gender, age, viral genotypes, infection transmission routes, and markers of HBV and HIV. Ter Arkh 2010; 82(3):52-6.
2. Bakr I, Rekacewicz C, El-Hosseiny M et al. Higher clearance of hepatitis C virus infection in females compared with males. Gut 2006; 55(8):1183-7.
3. Hayashi J, Kishihara Y,Ueno K et al. Age-related response to interferon-α treatment in women vs men with chronic hepatitis C virus infection. Arch Intern Med 1998; 158(2):177-81.
4. Bressler BL, Guindi M, Tomlinson G, Heathcote J. High body mass index is an independent risk factor for nonresponse to antiviral treatment in chronic hepatitis C. Hepatology 2003; 38(3):639-44.
5. Floreani A, Cazzagon N, Boemo DG et al. Female patients in fertile age with chronic hepatitis C, easy genotype, and persistently normal transaminases have a 100% chance to reach a sustained virological response. Eur J Gastroenterol Hepatol 2011; 23(11):997-1003.
6. 6)Villa E, Karampatou A, Cammà C et al. Early menopause is associated with lack of response to antiviral therapy in women with chronic hepatitis C. Gastroenterology 2011; 140(3), 818-29.
7. Langer C, Gansz B, Goepfert C et al. Testosterone up-regulates scavenger receptor BI and stimulates cholesterol efflux from macrophages. Biochem Biophys Res Commun 2002; 296(5):1051-7.

8. Scarselli E, Ansuini H, Cerino R et al. The human scavenger receptor class B type 1 is a novel candidate receptor for the hepatitis C virus. EMBO J 2002; 21(19): 5017-25 .
9. Hayashida K, Shoji I, Deng L, Jiang DP, Ide YH, Hotta H. 17β-estradiol inhibits the production of infectious particles of hepatitis C virus. Microbiol. Immunol 2010; 54(11):684-90.
10. Latt NC, Spencer JD, Beeby PJ et al. Hepatitis C in injecting drug-using women during and after pregnancy. J Gastroenterol Hepatol 2000;15(2):175-81.
11. Watashi K, Inoue D, Hijikata M, Goto K, Aly HH, Shimotohno K. Anti-hepatitis C virus activity of tamoxifen reveals the functional association of estrogen receptor with viral RNA polymerase NS5B. J. Biol. Chem 2007; 282(45):32765-72.
12. Rong X, Lu L, Wang J, Xiong H, Huang J , Chen J, et al. Correlation of viral loads with HCV genotypes: higher levels of virus were revealed among blood donors infected with 6a strains. PloS One 2012; 7: 12.
13. Iqbal S, Rahman KU, Sheikh MA etal. Response of different HCV genotypes to interferon therapy in different age groups of chronic hepatitis C patients. JAMC 2014; 26(3):310-5.
14. Belci P Collo A, Martorana M et al. Can gender predict virological response to standard antiviral therapy for chronic hepatitis C? A retrospective study. Hepatoma Res 2016; 2:122-30.