Original Article

Efficacy of Atorvastatin Plus Pegylated Interferon and Ribavirin Versus Pegylated Interferon and Ribavirin Alone in Chronic Hepatitis C Patients with Genotype-3a

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Abstract: Chronic hepatitis C infection has created a huge burden of disease causing serious health effects. The combination therapy used to treat hepatitis C virus (HCV) infection includes Pegylated interferon and Ribavirin. As cholesterol biosynthesis plays a pivotal role in HCV replication, the use of various statins has been associated with higher sustained viral response **Objective:** To compare the efficacy of atorvastatin plus pegylated interferon and ribavirin versus pegylated interferon and ribavirin alone in patients of chronic hepatitis C with genotype-3a **Methods:** This Randomized controlled trial was conducted at outpatient department, Mayo Hospital Lahore for six months i.e. May to November 2017. After ethical approval, 60 patients of ages 25 to 55 years of either gender with chronic hepatitis C with genotype 3a were included in the study. Informed consent was taken from all patients. Then patients were randomly allocated into two groups "A" and "B" using random number table. Patients in Group A received standard of care treatment for chronic hepatitis C i.e. pegylated interferon and ribavirin while the patients in Group B also received tab atorvastatin along with the standard treatment. Patients were follow up for 4 week. Blood samples were collected and HCV RNA detection. All this information were entered in proforma **Results:** In standard therapy group, the mean age of patients was 39.50±8.39years. In atorvastatin plus standard therapy group, the mean age of patients was 34.30±6.78years. In standard therapy group, there were 25 (83.3%) males and 5 (16.7%) females. In atorvastatin plus standard therapy group, there were 16 (53.3%) males and 14 (46.7%) females. After 4 weeks, Rapid Virological Response (RVR) was achieved in 4 (13.3%) patients in standard therapy group while in 14 (46.7%) in atorvastatin plus standard therapy group. The difference was significant ($p<0.05$) **Conclusions:** Atorvastatin in combination with Pegylated interferon and ribavirin have better efficacy as compared to Pegylated interferon & ribavirin alone in chronic hepatitis C-3a.

Key words: Atorvastatin, Chronic hepatitis C, Pegylated interferon, Ribavirin, Rapid viral response.

Introduction:

Hepatitis C virus infection has become a global burden by infecting around 110-170 million people worldwide [1-4]. Chronic HCV infection leads to chronic liver disease causing serious health affects like liver cirrhosis and hepatocellular carcinoma [3-5]. HCV shows a unique heterogenicity and has 7 genotypes and more than 67 subtypes [2]. This variability has significant clinical implications in the pathogenesis and the treatment of the infection. Genotype 1 and 3 are common globally, genotype 1 being the most common in Europe and America while in Pakistan it is the genotype 3 which is the commonest [6].

The combination therapy for HCV infection includes pegylated interferon and Ribavirin [3,7]. The best indicator for effective therapy is sustained viral response. The attainment of rapid

viral (RVR) response is highly predictive of achieving sustained viral response (SVR) [8]. Although this dual therapy has raised the sustained viral response up to 50%, newer treatment options are being considered to achieve better results. Both host and viral factors are responsible for poor SVR, among which the genotype and subtype plays a pivotal role [7-9]. Over the past decade other treatment options have been tried including drugs with direct anti-hepatitis C viral activity, or those acting against host enzymes essential for viral replication but it is a costly treatment [3,4,7,10].

Cholesterol biosynthesis plays a pivotal role in hepatitis HCV replication. Studies have shown that statins [(HMG-CoA) reductase inhibitors] inhibit the synthesis of cholesterol hence suppressing the replication of HCV. The use of various statins has been associated with higher sustained viral response [9, 10]. Seyam et al studied the effect of Fluvastatin in combination with standard of care therapy for HVC in Egyptian population and concluded that those patients who received Fluvastatin along with standard of care therapy achieved higher SVR (8 out of 21 patients receiving Fluvastatin achieved SVR as compared to 3 out of 23 patients on control group with p= 0.08) as well as higher rapid viral response (RVR) (53.3% patients receiving fluvastatin achieved RVR as compared to 44.4% patients in control group with p = 0.02) [10]. Another study done by Milazzo et al., significantly higher RVR rate was attained in the fluvastatin arm and compared with standard therapy (33% vs. 4% respectively, p=0.02)[11].

As the hepatitis C genotype 3a is most prevalent in Pakistan & is different from other countries, so we wanted to evaluate the effect of adding atorvastatin to the standard therapy for chronic hepatitis C in achieving rapid virological response so we might be able to achieve better treatment response to HCV infection and reduce the burden of this infection in our country.

Methods:

This Randomized controlled trial was conducted at outpatient department of medicine, Mayo Hospital Lahore for six months i.e. May to November 2017.After ethical approval 60 patients of chronic hepatitis C with genotype-3a, of ages 25 to 55 years with either gender were included by Non-probability consecutive sampling. Sample size was calculated with 80% power of test, 95% confidence level and taking expected percentage of efficacy of atorvastatin plus pegylated interferon and ribavirin as 33% and pegylated interferon and ribavirin alone as 4%.Patients with chronic liver disease, autoimmune hepatitis, diabetes mellitus, hypertension, dyslipidemias, Allergy to statins, Concomitant HBV infection & malignancy were excluded from the study. After informed consent, these patients were randomly allocated into two groups “A” and “B” using random number table. Patients’ identity was kept confidential. Risks and benefits were explained to the patients. All subjects were interviewed for demographic information such as name, age and gender. Patients in Group A receive standard of care treatment for chronic hepatitis C i.e. pegylated interferon and ribavrin while the patients in Group B also receive tab atorvastatin (20 mg) along with the standard of care treatment for chronic hepatitis C. Patients were called for follow up at fourth week of the start of therapy. Blood samples were collected and HCV RNA detection with PCR was carried out. Efficacy was labeled as undetectable viral RNA at the end of fourth week of therapy using polymerize chain reaction (PCR). All this information was entered in the predesigned proforma. All the data was entered and analyzed in SPSS version 15.0. Quantitative variables like age and duration of hepatitis were presented as mean and standard deviation. The Qualitative variables like gender and presence or absence of Hepatitis were presented as frequency and percentages. Both groups were compared by applying chi-squarer test with p-valule≤0.05 as significant. Data was stratified for age, gender and duration of HCV to address effect modifiers. Post-stratification, chi-square test was applied with p-value ≤0.05 as significant.

Results:

In standard therapy group, the mean age of patients was 39.50±8.39 years. In atorvastatin plus standard therapy group, the mean age of patients was 34.30±6.78 years. In standard therapy group, there were 25 (83.3%) males and 5 (16.7%) females. In atorvastatin plus standard therapy group, there were 16 (53.3%) males and 14 (46.7%) females. So, there were a total of 30 patients in each group (Table 1). In standard therapy group, the mean duration of HCV was 3.37±1.63months. In atorvastatin plus standard therapy group, the mean duration of HCV was 3.40±1.45months. After 4 weeks, there were 26 (86.7%) patients who had HCV 3a in blood on PCR in standard therapy group while in 16 (53.3%) in atorvastatin plus standard therapy group (Table 2). The difference was significant (p<0.05).After 4 weeks, RVR was achieved in 4 (13.3%) patients in standard therapy group while in 14 (46.7%) in atorvastatin plus standard therapy group. The difference was significant (p<0.05).Data was stratified for age of patients. In patients aged 25-40years, RVR was achieved in 1 (6.7%) patients in standard therapy group while in 9 (39.1%) in atorvastatin plus standard therapy group. The difference was significant (p<0.05). In patients aged 41-55years, RVR was achieved in 3 (20%) patients in standard therapy group while in 5 (71.4%) in atorvastatin plus standard therapy group. The difference was significant (p<0.05).Data was stratified for gender of patients. In males, RVR was achieved in 1 (4.0%) patients in standard therapy group while in 6 (37.5%) in atorvastatin plus standard therapy group. The difference was significant (p<0.05). In females, RVR was achieved in 3 (60%) patients in standard therapy group while in 8 (57.1%) in atorvastatin plus standard therapy group. The difference was insignificant (p>0.05) (Table 3).

Data was stratified for duration of HCV. In patients with HCV from 1-3months, RVR was achieved in 0 (0%) patients in standard therapy group while in 10 (52.6%) in atorvastatin plus standard therapy group. The difference was significant (p<0.05). In patients with HCV from 4-6months, RVR was achieved in 4 (24%) patients in standard therapy group while in 4 (36.4%) in atorvastatin plus standard therapy group. The difference was insignificant (p>0.05).

		Group	
		Standard therapy	Atorvastatin plus standard therapy
Age (years)	n	30	30
	Mean	39.50	34.30
	Standard deviation	8.39	6.78
	Minimum	27	25
	Maximum	54	49

Table 1: Descriptive statistics of age of patients

		Group		Total
		Standard therapy	Atorvastatin plus standard therapy	
HCV 3a on PCR	Present	26	16	42
		86.7%	53.3%	70.0%
	Absent	4	14	18
		13.3%	46.7%	30.0%

Total	30	30	60
	100%	100%	100%

Table 2: Comparison of PCR, Chi-Square Test = 7.937, P-value = 0.005 (Significant), Findings after 4 weeks

		Group		Total
		Standard therapy	Atorvastatin plus standard therapy	
RVR	Yes	4	14	18
		13.3%	46.7%	30.0%
	No	26	16	42
		86.7%	53.3%	70.0%
Total		30	30	60
		100%	100%	100%

Table 3: Comparison of RVR in both groups, Chi-Square Test = 7.937, P-value = 0.005 (Significant)

Discussion:

HCV infection is a well-known entity all over the world now. This infection, which most commonly takes a chronic course, is a global menace and has not only become a big cause of morbidity and mortality but has also added to economic burden. HCV is a blood borne infection. Unscreened blood and blood products, use of contaminated needles, unsterilized surgical instruments especially in unsafe dental practices in under develop countries are common sources of HCV spread [1].

It has been estimated that globally 130 to 180 million people are infected with HCV which makes approximately 2-3% of the world population. The figure of ten million people of Pakistan being infected with HCV gives a fair idea of the extent of this peril in our country. According to one study, more than 350,000 people die of complications associated with chronic HCV infection each year all over the world [12,13].

World Health Organization (WHO) has described 11 genotypes of HCV. Genotype 1 is the most prevalent type, followed by 3, 2, 4 and 6. Genotype 3 the most prevalent form in south east Asia [14,15]. Chronic HCV infection has both hepatic and extra hepatic manifestations. Among the hepatic manifestations, cirrhosis and hepatocellular carcinoma are at the top. Majority of the deaths caused by HCV infection are due to these two complications. Globally, 27% cases of cirrhosis and 25% cases of hepatocellular carcinoma are believed to be the result of chronic HCV infection. However, various extrahepatic manifestations of chronic HCV add to the morbidity and even mortality of the patient. Association of chronic HCV infection and enhanced atherosclerosis has been reported in literature, thereby increasing the risk of death by IHD and stroke [12].

Liver is the center for cholesterol homeostasis in human body. Also it is the principle organ infected by HCV. Hence an overlap between HCV life cycle, infection and lipid metabolism can be expected. Decades of research has shown that the HCV and lipids has a unique relationship. Chronic HCV infection at one end is responsible for the dyslipidemias in the patients and the virus needs these lipids for the replication of its own RNA at the other end. Not only this, but the lipids also play a crucial role in infecting the hepatocytes [16-20]. This discovery lead to the presumption that if lipids are necessary for the replication of HCV, the use of the drugs that block

the pathway of lipid synthesis might be useful in controlling the viral replication in patients suffering from chronic HCV infection. Thus a whole new horizon has opened with researches going on regarding this new approach for the treatment of chronic HCV infection.

Our study is based of the fact that HCV replication needs lipids. We conducted a randomized controlled trial to assess the effect of addition of atorvastatin, a competitive HMGCoA inhibitor, to the standard of care regimen for the treatment of chronic HCV infection in patients having genotype 3a. Larger number of patients (36%) who receive atorvastatin in addition to pegylated interferon and ribavirin were successful in achieving RVR as compared to only 16% of the patients in the other group who received only pegylated interferon with ribavirin. This difference is statistically significant with a p value of 0.023.

Studies have shown that those patients who achieve RVR have a higher probability of achieving SVR. Only a small number of patients have a reappearance of detectable viral RNA after it has disappeared after four week of therapy [21, 22]. Hence, achieving RVR can be labeled as a good indicator of achieving SVR in patients with chronic HCV infection. The results of our study were comparable to the study carried out by Milazzo *et al.* In their study, 33% of the patient in statin group achieved RVR as compared to only 4% of the patients in the standard therapy group [11]. However they used fluvastatin in stead of atorvastatin. Also the patient population they selected was different from ours. The patients in their study were co infected with HIV while our patients were not.

Seyam et al studied the effect of addition of fluvastatin to the standard of care therapy for chronic HCV infection in Egyptian population. They evaluated all the parameter including RVR, EVR, cEVR, ETR and SVR. Virological responses in the study group were higher as compared to controlled group but none was statistically significant with the exception of complete EVR which was significantly higher in study group [23]. Eric Yoshida in his article mentioned the work carried out by Malaguarnera *et al.*, the team studied the role of rosuvastatin in chronic HCV infection. The number of patients in study group achieved statistically significant higher SVR as compared to those in the placebo group. However, majority of patients in this study were suffering from HCV with genotype 1 as compared to our study which included patients with genotype 3a [24].

Deelang *et al.*, concluded in their study that statins do potentiate the activity of HCV inhibitors. They also proposed that the use of statins may also delays or prevent the development of resistance of HCV against various anti viral agents. The study showed that Lovastatin, mevastatin, simvastatin, and fluvastatin inhibited HCV replication in vitro. However, pravastatin was devoid of any such activity [25]. Harrison et al evaluated IDEAL trial in a retrospective manner. 66 out of 3070 patients were on statins and they achieved higher SVR as compared to patients who were not receiving statins with a p value of 0.02 [26]. *Ikeda et al.*, evaluated the antiviral activity of five statins namely atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin. Their results showed that fluvaststin posses highest anti viral activity. Atorvastatin and simvastatin exhibit intermediate antiviral effects while lovastatin showed low antiviral activity [27].

O'Leary et al carried out a pilot clinical trial on the antiviral effects of atorvastatin and concluded that at conventional doses, atorvastatin has no antiviral activity against HCV. Their study included only 10 patients, having genotype 1 of HCV. All the patients were hypercholestremic and were given only atorvastatin to determine its antiviral effects. None of the patients was to receive standard therapy for HCV infection in the coming three months after the start of the trial. Also, the patients who had received the treatment for chronic HCV infection in the past three months were excluded from the trial [28].

A retrospective study carried out by Forde *et al.*, also showed that statins do not show significant

anti-viral effects in vitro. They concluded that the difference between the results of in vitro and in vivo studies can be attributable to several factors, one of which could be the lower achievable levels of statins in vivo as compared to much higher levels in the culture media [29].

It can be seen that most of the patients in previous studies were infected with genotype 1. Also, they received treatment with fluvastatin whereas; patients included in our study were infected with HCV-3a (strain common in Pakistan) and were given atorvastatin. Hence, our study is the first of its kind in this regard. However, we only evaluated the response of atorvastatin on RVR. For more precise evaluation of the role of atorvastatin in chronic HCV infection, their response on SVR needs to be seen. Also, due to limited work done on this aspect of atorvastatin on genotype 3a, further work need to be done so that our population can benefit from the potentially useful aspect of this drug while on therapy for the chronic HCV infection. As a concluding remark, we can say that Statins are on horizon for being used as an adjunct for the treatment of chronic HCV infection.

Conclusions: It can be concluded that atorvastatin in combination with pegylated interferon and ribavirin have better efficacy as compared to pegylated interferon & ribavirin alone for HCV-3a infection.

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