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Statins Added to Chronic Hepatitis C Treatment: Is it Beneficial?

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Abstract

Objectives: Chronic hepatitis C (CHC) is a major health problem in Egypt with about 9.8% of Egyptian population having an active hepatitis C infection. Almost Every step in the Hepatitis C virus (HCV) life cycle is closely related to lipid metabolism. HCV circulate in the body in lipid-rich particle, attach to hepatocytes via lipoprotein receptors. Recent attention focused on HMG CoA Reductase inhibitors (statins) and their potential therapeutic role in hepatitis C.

Methods: This retrospective closed cohort study included 60 naïve CHC patients. The HCV statins group patients (n = 26) received the combination of Standard of care (Interferon alfa and repavirin) and fluvastatin 80 mg daily; HCV non statins group (n = 43) treated with the SOC treatment only. Both groups receive their treatment over a duration of 48 weeks.

Results: On-treatment viral responses as well as the SVR were significantly better in HCV statins group in comparison to HCV non statins group; rapid virological response (RVR), early virological response (EVR) and sustained virological response (SVR) were (13.3%, 73.3% and 68.3%) in HCV statins group vs. (0%, 58.8% and 52.9%) HCV non statins group with p value 0.00, 0.003 and 0.003 respectively. Multivariate logistic regression model identified statins use as a significant predictor of an SVR.

Conclusion: A combination of fluvastatin and SOC significantly improved the SVR in naïve CHC Egyptian patients. Further powered randomized control trails are needed to elucidate statins role in HCV treatment.

Keywords: HCV-treatment; Statins; Response

Aim

The primary aim of the study was to assess the efficacy of adding statins to SOC therapy (PEG IFN/ribavirin) on the on-treatment virologic response as well as on SVR in CHC naïve Egyptian patients.

Introduction

Chronic hepatitis C (CHC) is a major worldwide medical problem. According to the WHO 130-170 million people are chronically infected with HCV (~3% of the world's population), that it infects 3-4 million people per year, >10% of these people will develop liver cirrhosis or cancer over time and that more than 350,000 people die from hepatitis C related diseases each year [1].

About 50-80% of patients with primary HCV infection develop chronic infection; about 25% of patients with chronic infection develop cirrhosis within 10-30 years; and 5-10% of patients with cirrhosis develop hepatocellular carcinoma (HCC) [2].

In Egypt, HCV infection is a major health problem with estimated prevalence about 22% making it accounts for most chronic liver disease and hepatocellular carcinoma (HCC) cases in our country [3].

For years, combined interferon α and ribavirin has been the standard of care therapy (SOC) for chronic hepatitis C [4]. As a result of adverse events, a moderate rate of virologic response, and high costs associated with HCV therapy, finding early markers of sustained treatment response is a clinical priority [5]. The most potent pretreatment factors for sustained virological response (SVR) were viral genotype, baseline serum viral load, age, gender, BMI, stage of liver fibrosis and it was found that genetic polymorphisms for interleukin 28B located on chromosome 19 also affects SVR [6,7].

Several studies have shown that components of cholesterol-biosynthetic pathways play an essential role in HCV replication, especially geranylgeranyl that is needed for HCV replication. It has been demonstrated that statins (3-hydroxyl-3-methylglutaryl-coenzyme A reductase inhibitors) interrupt HCV-RNA replication in cultured hepatocytes [8,9]. Combining statins to SOC therapy had a synergistic inhibitory effect on HCV replication [10] resulting in

improvement of early virological response (EVR), rapid virological response (RVR) as well as SVR without additional adverse effect [11].

Materials and Methods

Study population

This retrospective closed cohort study included 60 adult (18-60 years old) Egyptian patients of both genders with chronic HCV infection who were diagnosed by anti-HCV antibodies, HCV-RNA in addition to the histological evidence of chronic hepatitis. Patients were recruited from outpatient's clinic of National Hepatology and Tropical Medicine Research Institute (NHTMRI) and Ahmed Maher Teaching Hospital, Cairo, Egypt from August 2012 July 2014. The study protocol was approved by the National Committee for Control of Viral Hepatitis, Ministry of Health and Population (MOHP), Egypt.

An inclusion criterion was done according to the National Committee for Control of Viral Hepatitis, MOHP. Patients were excluded if they had contra-indications to Peg-IFN/RBV therapy (e.g. leukocyte count <3,000/mm^3, platelet count <75,000/mm^3, hemoglobin <13 g/dl for men and <12 g/dl for women, decompensated cirrhosis, uncontrolled thyroid disease, autoimmune disease, malignant neoplastic diseases, severe depression, other psychiatric disorders or active substance abusers) poorly controlled diabetes, body mass index; BMI>30 kg/m^2.

After signing the informed consent, all patients had been scheduled to receive the SOC therapy in the form of PEG-IFN alpha 2a or 2b plus weight-based ribavirin (RBV); 15 mg/kg for duration of 48 weeks. Patients were assigned to treatment groups in accordance to indication for statins therapy:

Group (1) HCV-statins group (n = 24): Naïve chronic HCV patients who are assigned to receive PEG-IFN alpha 2a 180 µg/week SC- or 2b 1.5 mg/kg/week SC plus weight-based RBV therapy; daily dose of 1000 mg for patients with body weigh ≥75 kg or 1200 mg for patients who weighed <75 kg) in addition to statins therapy. Statins therapy in the form of oral fluvastatine (80 mg/day was given as a primary prevention of cardiovascular disease (CVD) in high or moderate risk groups; such as old age, diabetes mellitus, and hypertension; with no overt clinical evidence of CVD [12-14].

Group (2) HCV non-statins group (n = 36): Naïve chronic HCV who are assigned to receive PEG-IFN plus weight-based RBV therapy without documented statins exposure during the evaluation period. All of them were of low risk patients with no overt clinical evidence of CVD [12-14].

Data collection

Demographic data (age, gender, body mass index (BMI), hematological tests, liver biochemical profile [serum alanine aminotransferase (ALT); aspartate aminotransferase (AST); gamma-glutamyl (GGT), total bilirubin (Bil), alkaline phosphatase], synthetic liver function such as serum albumin (Alb), international normalized ratio (INR), lipid profile (fasting serum cholesterol, triglyceride, low density lipoprotein (LDL), high density lipoprotein (HDL) in addition to renal function tests which were measured by using synchron CX4-clinical system, alfa-fetoprotein (AFP) and Thyroid Stimulating Hormone (TSH) using Axyam machine-Irelan at baseline then 24 weeks after completion of treatment.

HCV-PCR was evaluated using Real Time PCR (Stratagene) at baseline and after 4 and 12 weeks on treatment, Thereafter HCV-RNA PCR was evaluated at week 24 after completion of treatment. Liver biopsies were interpreted according to the Metavir scoring system [15] by a single experienced pathologist.

Medical records were then reviewed to identify the data regarding statins therapy including type, dose, duration, patient compliance, side effects and response retrieved.

Statistical analysis

Data were collected, checked, revised and entered the computer. Data analyzed by SPSS statistical package version 19. Excel computer program was used to tabulate the results, and represent it graphically.

For the quantitative variables, which are normally distributed, independent t-test used to declare the significant difference between the two groups (HCV statins group and HCV non statins group) at $p<0.05$.

Paired t-test used to declare the significant difference between before and after treatment period at $p<0.05$.

Pearson's correlation coefficient used to declare the significant correlation between the quantitative parameters within each group at $p<0.05$.

Qualitative variables were expressed as count and percentages. Difference between 2 proportions test used to show the significant difference between the two groups (HCV statins group and HCV non statins group) at $p<0.05$ [16].

Univariate and Multivariable, logistic regression analysis was used to identify baseline factors that were predictors of SVR. P values based on the logistic regression model, odds ratios (ORs), and 95% confidence intervals (CIs) for the ORs were reported for factors that were significant ($P<0.05$).

Results

Patients characteristics

The retrospective closed cohort study enrolled 60 treatment naïve chronic hepatitis C patients: 26 treated with SOC treatment in addition to statins, and 34 controls treated with SOC treatment only.

All included patients completed 48 weeks of PEG-IFN/RBV treatment with no reported clinically significant side effects, no dose modification needed or withdrawal. HCV-statins group received fluvastatin 80 mg daily. 3 patients reported mild myalgia and headache during treatment period.

All study participants were subjected to 24 weeks of follow up after cessation of therapy. Table 1 shows the baseline patient characteristics of the two groups.

Variable	HCV-statins group (n = 26)	HCV-non statins group (n = 34)	Total number (n = 60)	P value
Male sex	11 (42.3%)**	26 (76.5%)**	37/60 (61.7%)**	0.007
Age (years)	39.39 ± 1.51	41.18 ± 1.38	40.40 ± 7.89	0.388
BMI*	25.8 ± 1.76	27.61 ± 1.66	26.83 ± 9.38	0.459
Albumin (3.2-4.8 g/dl)	3.95 ± 0.06	3.77 ± 0.05	3.85 ± 0.322	0.038
Total bilirubin (0-1.2 mg/dl)	0.94 ± 0.06	1.05 ± 0.07	1.008 ± 0.397	0.275
HCV RNA×10^6(IU/ml)	260×10^6 ± 160×10^6	3420×10^6±2320×10^6	2060×10^6 ± 10300×10^6	0.184
AST (0-34 U/L)	56.96 ± 3.15	64.32 ± 4.53	61.133 ± 22.667	0.188
ALT (0-49 U/L)	65.61 ± 5.09	57.82 ± 2.82	61.2 ± 21.292	0.189
Cholesterol (0-200 mg/dl)	283.92 ± 13.13	277.52 ± 8.7	280.3 ± 57.898	0.687
Triglycerides (0-150 mg/dl)	260.46 ± 10.52	278.91 ± 9.58	270.917 ± 55.257	0.2
HDL	51.19 ± 1.85	51.2 ± 1.44	51.2 ± 8.812	0.995

*BMI: Body Mass Index (calculated as weight in kg/height in m^2); HDL: High Density Lipoproteins

**Values are expressed as mean ± SE for continuous variables and number of patients (%) for categorical variables

Table 1: The baseline clinical and laboratory data of all included patients.

Virologic response rates; rapid virological response (RVR), early virological response (EVR) and sustained virological response (SVR) were significantly higher in HCV-statins group in comparison to HCV non-statins group; [(13.3%, 73.3% and 68.3%) vs. (0%, 58.8% and 52.9%) with p value 0.00, 0.003 and 0.003 respectively (Figure 1).

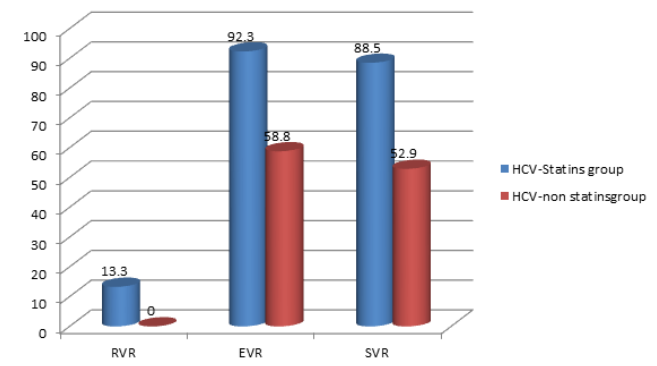

Figure 1: Response rates RVR, rapid virological response at week 4; EVR, early virological response at week 12 and SVR, sustained virological response at week 24 after cessation of therapy.

Follow up laboratory values

Both groups of patients showed significant reduction in mean ± SD of their ALT and AST at the end of treatment compared to baseline values (p value = 0.000). HCV-statins group of patients had additional statistical significant reduction of their total cholesterol, triglycerides and HDL at the end of treatment compared to baseline (p value = 0.000) such significant reduction was not observed in HCV-non statins group. As shown in Table 2.

Virological and biochemical response

A preliminary comparison of the main SVR predictor balance between the two groups was performed using univariate and multivariate testing of the following: Age, gender (female/male), BMI, statins use, baseline ALT, low/high viral load (≤400,000 IU/ml/ >400,000 IU/ml), baseline low-density lipoprotein baseline triglycerides, and High density lipoproteins.

At univariate analysis a statistical significant correlation was found between SVR and statins use; The HCV statins group arm showed odds ratio of (6.8) for having SVR compared to HCV non statins arm with p value of (0.006).

In multivariate logistic regression model for the outcome SVR and statins use as predictor adjusting for the baseline main predictors of virological response (Age, gender, BMI, baseline ALT, baseline low/ high viral load (≤400,000 IU/ml/>400,000 IU/ml), baseline low-density lipoprotein, baseline triglycerides, and High density lipoproteins), statins use was much more significantly associated with SVR with odds ratio of (15.4) and p value of (0.003) (Table 3).

Variable	HCV-statins group (n = 26)			HCV- non statins group (n = 34)		
	Baseline	EOT	P value	Baseline	EOT	P value
AST	56.96 ± 3.15	37.19 ± 2.24	0.000*	64.32 ± 4.53	49.67 ± 4.42	0.053
ALT	65.61 ± 5.09	32.61 ± 1.3	0.000*	57.82 ± 2.82	38.35 ± 2.05	0.000*
Cholestrol	283.92 ± 13.13	197.23 ± 7.92	0.000*	277.52 ± 8.7	280.11 ± 8.85	0.337
TG	260.46 ± 10.52	183.38 ± 6.96	0.000*	278.91 ± 9.58	274.67 ± 9.69	0.173
HDL	51.19 ± 1.85	183.38 ± 6.96	0.000*	51.2 ± 1.44	274.67 ± 9.69	0.000*

* Clinically significant; EOT: End of Treatment

Table 2: Follow up laboratory values for HCV-statins group and HCV-non statins group.

Univariate logistic regression			
Predictor	**OR**	**95% CI**	**P value**
Age	1.06	0.99-1.144	0.099
Gender (female vs. male)	1.53	0.49-4.85	0.47
BMI	1.02	0.96-1.09	0.478
Treatment arm (statins versus standard therapy)	6.81	1.72-27.05	0.006
ALT	1.03	0.998-1.07	0.06
Baseline HCV-RNA, IU/mL (400000 vs. 400000)	1.57	0.51-4.817	0.43
Baseline cholesterol mg/dL	1.00	0.99-1.00	0.96
Triglycerides	0.995	0.99-1.00	0.42
HDL	0.9799746	0.92-1.04	0.52
Multivariate logistic Regression			
Outcome SVR and predictor statins use adjusted for baseline predictors of SVR	15.36	2.46-95.79	0.003

Table 3: Pre-treatment variables associated with SVR at univariate and multivariate analysis.

Discussion

The main target of treatment of HCV patients is to eradicate hepatitis C virus RNA, which is predicted by the attainment of SVR which is associated with 99% opportunity of being HCV RNA negative during long-term follow-up [17] as well as decreases in all HCV related mortality, liver-related death, the need for liver transplantation, hepatocellular carcinoma rates, and liver-related complications [18-21].

It is well known that HCV replication process can be disrupted by treatment with inhibitors of 3-hydroxy-3-methyglutaryl CoA (HMGCoA) reductase such as the statins [8,22]. Thus statins may represent an interesting adjuvant to SOC to improve the sustained virological response (SVR) in HCV patients receiving combination antiviral therapy [23,24].

The most important finding in this retrospective closed cohort study is that the response to triple treatment with fluvastatin 80 mg daily oral supplementing the standard PEG-IFN/ribavirin in 24 patients infected with chronic HCV is significantly much better than the response to standard PEG-IFN/ribavirin in 36 HCV patients; RVR, EVR and SVR in those received triple therapy were 13.3%, 73.3% and 68.3% respectively which were significantly higher than that (0%; 58.8%; and 52.9%) of the patients who did not receive adjuvant statins therapy. Our multivariate logistic regression analysis revealed that statin use was the only predictor for SVR. In agreement with our results Sezaki et al. [25], Georgescu et al. [26] and Kondo et al. [27] who had demonstrated the addition of fluvastatin 20 mg daily to SOC treatment significantly improved the SVR in patients infected with HCV genotype 1b.

Statins were found to interfere with the replication of HCV through a precise mechanism of the anti-HCV activities of statins that is described in recent studies. It was suggested that Statins inhibit the de novo synthesis of cholesterol in the liver by blocking mevalonate production via inhibition of 3-hydroxy-3-methylglutaryl CoA reductase (HMG CoA reductase) and have other pleiotropic effects. In combination to IFN-a, fluvastatin show strong synergistic activity and enhance the anti-HCV effect of IFN-a [10,28].

In our study, the tolerability of the two treatment schedules was similar, confirming previous data on the safe use of statins in HCV infected patients [29].

In agreement with previous reports studying the use of statins in chronic hepatitis C, our results suggest that statins are efficient to use in patients with CHC who are scheduled for therapy with PEG-IFN and RBV. No significant differences in adverse events were recorded.

In conclusion, our study concluded that the use of statins improve SVR when they are added to standard PEG-IFN and RBV therapy.

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