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Evaluation of fluvastatin in combination with the standard of care therapy (PEG-IFN/Ribavirin) in Egyptian patients with hepatitis C virus

LIVER

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Original Article

ABSTRACT

Background/Aims: Cholesterol biosynthesis suppresses the replication of HCV-1b replicons, thus influencing hepatitis C virus (HCV) natural history. This study aimed at comparing the efficacy and safety of fluvastatin (FLV) as an adjuvant therapy to the standard of care (SOC) therapy, i.e., pegylated interferon (PEG-IFN) and ribavirin, for the treatment of HCV patients.

Materials and Methods: Sixty HCV patients were enrolled and allocated to either group I, who received the triple therapy (fluvastatin + SOC), or group II, who received SOC; the duration for both treatments was 48 weeks. All patients were subjected to pretreatment liver biopsy and monthly biochemical tests (liver profile, CBC), and quantitative HCV-RNA test was performed at weeks 0, 4, 12, 48, and 72.

Results: All virological responses were higher in group I than in group II, with no statistical difference. Group I showed no manifestations of hepatotoxicity.

Conclusion: Fluvastatin yielded a borderline, significantly higher complete early virological response than SOC; therefore, it is a safe adjuvant to the SOC therapy.

Keywords: Hepatitis C virus, standard of care, fluvastatin, rapid virological response, early virological response, sustained virological response

INTRODUCTION

Hepatitis C virus genotype 4 (HCV-4) is the most common genotype in Africa and the Middle East, particularly in Egypt. HCV-4 has become the most resistant genotype to the standard of care (SOC) therapy, which involves a combination of pegylated interferon (PEG-IFN) and ribavirin; therefore, new treatment strategies for HCV-4 patients are required (1). Since the last decade, the identification of new therapeutics with direct anti-hepatitis C viral activity, such as polymerase and protease inhibitors, or against host enzymes essential for viral replication has become important. Cholesterol biosynthesis plays a critical role in hepatitis C viral replication in vitro (2,3). Moreover, statins [3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors], inhibiting the synthesis of cholesterol, suppress the replication of HCV-1b replicons (4). This has been verified by transfection experiments involving cultured hepatocytes, whether alone or combined with IFN. Moreover, the five known statins that have been well studied reportedly shown different extents of inhibition; the most and least potent of them being fluvastatin (FLV) and pravastatin, respectively (5). FLV monotherapy, at a daily therapeutic dose of 80 mg, suppressed serum HCV RNA by a log of 1.75 (6), which was not achieved with atorvastatin at a daily dose of 20 mg (7). Thus, this study aimed to explore the efficacy and safety of FLV as an adjuvant therapy to SOC therapy in Egyptian HCV patients infected with HCV-4.

MATERIALS AND METHODS

This prospective study was conducted at the Hepatology Clinic of the Arab Contractor Medical Centre (ACMC) from January 2011 to January 2013. The study was approved by the institutional ethical committee, and all patients provided an informed consent. Sixty chronic

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HCV patients were randomly enrolled according to the following inclusion criteria: i) serum HCV-RNA detection by RT-PCR, ii) naïve to HCV treatment, iii) age >18 years and <60 years, and iv) a normal complete blood count (CBC). The exclusion criteria were as follows: i) refusal to sign an informed consent, ii) Metavir score stage of 0 or 4 fibrosis, iii) poorly controlled diabetes or hypertension, iv) uncontrolled systemic disease (renal, cardiac, pulmonary), v) deranged thyroid function, vi) malignancy, vii) autoimmune hepatitis, viii) pregnancy or expected to become pregnant during and for 6 months after cessation of therapy, ix) alanine aminotransferase (ALT) >fivefold the upper limit of the normal range, x) a history of adverse reaction to any HMG-CoA reductase inhibitor, and xi) concomitant chronic hepatitis B virus infection.

Patients were randomly divided into two groups:

Group I: Thirty patients who received SOC (PEG-IFN alpha-2a at a dose of 180 µg subcutaneously weekly in combination with oral ribavirin 1,000 mg daily if body weight was <75 kg or 1,200 mg daily if body weight was >75 kg) plus FLV at a dose of 80 mg/day.

Group II: Thirty patients who received SOC only and at the same doses as those described above.

All patients were subjected to the following events every 4 weeks for 48 weeks: i) Complete noting and evaluation of history and a thorough monthly clinical examination; ii) pretreatment laboratory workout, including CBC, liver biochemical profile [(LBP), bilirubin, ALT, and aspartate aminotransferase (AST)], albumin and prothrombin time, lipid profile [high density lipoprotein (HDL), total cholesterol (TC), triglycerides (TGD), and low density lipoprotein (LDL)] after an overnight fasting of 12 h, quantitative HCV-RNA was performed by applying the Abbott real-time HCV assay, characterized by the detection limit of 10 IU/mL; iii) abdominal ultrasonography; and iv) a percutaneous liver biopsy for histopathological examination using a disposable Guillotine biopsy needle 16G 20 cm (Italy) with specimens evaluated by Metavir scoring for activity grading and fibrosis staging (8).

HCV-RNA quantification by RT-PCR was performed at week 24 after cessation of therapy. Virological responses, i.e., rapid virological response (RVR), early virological response (EVR), end of treatment response (ETR), and sustained virological response (SVR) were evaluated, as defined by AASLD 2009 (9).

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) (SPSS Inc. Version 17, 2008, Chicago, IL, USA) was used for data analysis. Mean±standard deviation (SD) was used to describe quantitative data, while numbers and percentages were used to express categorical or qualitative data. The chi-square test was applied to test for correlation between two independent parameters. The independent-samples t-test and paired-samples t-test were used to compare means. The Friedman test was used as a non-parametric test (mean rank). Fisher's exact test and the Mann–Whitney U test (univariate analysis) were performed for a comparison of baseline characteristics and treatment outcome, i.e., various virological response rates (RVR, EVR, ETR, and SVR) between groups I and II. Probability (p) value is considered statistically significant when <0.05 and highly significant when <0.001.

RESULTS

The study comprised 60 patients who were divided into two groups: group I included 30 patients who received SOC therapy plus FLV. One patient in this group discontinued FLV at week 24 because of significant ALT elevation and continued treatment with SOC only. Another patient in group I discontinued treatment at week 28 because of retroperitoneal infection and perioneal fluid collection, which was surgically drained; it is notable that this patient's HCV-RNA test was negative at week 24 and 6 months after cessation of therapy. Group II included 30 patients receiving only SOC. Two patients dropped out from the study, including one who refused to continue treatment at week 8 because of flu-like symptoms and irritability, and one patient was lost to follow up after week 12.

Demographic features and pretreatment laboratory results, including histopathological examination, of the remaining 57 patients are summarized in Table 1. None of the laboratory tests had any statistically significant relation to any of the two groups.

The rates of various virological responses in the two studied groups are illustrated in Figure 1. All virological responses were higher in group I than in group II, with no statistical significance except for complete EVR (cEVR), which showed a borderline significant value (p=0.05), being higher in group I (26/30 patients; 86.7%) than in group II (19/27 patients; 70.4%).

Monitored transaminases and bilirubin in patients who completed the treatment in both groups are illustrated in Figure 2. Transaminases showed a highly significant gradual improvement in both groups along the treatment course and 6 months after treatment compared with the pretreatment levels (p<0.001). One patient from group I (0.03%) discontinued FLV at week 24 because of a fivefold rise in ALT level, and the patient continued treatment with SOC only. Bilirubin showed a highly significant rise (p<0.001) over the first 2 weeks of treatment, followed by a gradual highly significant improvement (p<0.001) in both groups.

CBC showed a highly significant decrease in all parameters, comparably in both groups, along the course of treatment till 6 months after treatment (p<0.001). In contrast, there was a highly significant improvement (p<0.001) in these indices, comparably in both groups, 6 months after cessation of therapy.

A patient from group I discontinued treatment by week 28 because of retroperitoneal infection and collection, which was drained surgically.

Table 1. Demographic features and pretreatment laboratory results of the two study groups

	Demographic features		Group I n=30 patients	Group II n=27 patients	p	Total n=57 patients
Age (years)		Mean±SD	48.9±5.8	45.5±8.68	0.08	47.2±7.45
	≤40/>40 years		2/28	7/20	**0.04**	9/48
Gender	**Male/Female**		30/0	26/1	0.29	56/1
Residence	**Urban/Rural**		13/17	10/17	0.64	23/34
Smoking					0.194	35/22
	Non-Smoker/Smoker		16/14	19/8		
BMI		Mean±SD	28.20±3.13	28.50±3.65	0.736	28.34±3.36
	Normal/Overweight/Obese†		5/16/9	4/12/11	0.498	9/28/20
Laboratory results						
	HCV RNA (× 10^6 IU/mL)	Mean±SD	0.9813±1.1290	1.2918±1.8226	0.438	1.1284±1.4923
Viral load	**Low** (<800 × 10^3 IU/mL) / **High** (≥800 × 10^3 IU/mL)		16/14	14/13	0.913	30/27
CBC	**Hb.** (13–17 g/dL)		15.10±1.53	15.18±1.02	0.823	15.14±1.3
Mean ± SD	**Plts.** (150–400 × 10^3 cells/mm^3)		209.46±55.85	225.59±54.16	0.274	217.10±55.16
	TLC (4–11 × 10^3 cells/mm^3)		6.77±1.64	6.67±1.93	0.835	6.72±1.77
LBP	**ALT** (≤40 U/L)	Mean±SD	63.53±31.90	70.96±43.45	0.462	67.05±37.65
	Normal/High		8/22	7/20	0.951	15/42
	AST (≤37 U/L)	Mean±SD	48.50±16.51	46.33±20.76	0.663	47.47±18.5
	Normal/High		7/23	9/18	0.411	16/41
	Albumin (3.5–5 g/dL)	Mean±SD	4.37±0.29	4.43±0.29	0.474	4.40±0.29
	Bil. (0.3–1.1 mg/dL)	Mean±SD	0.83±0.28	0.69±0.30	0.078	0.76±0.3
Lipid profile	**TC** (115–200 mg/dL)	Mean±SD	155.9±31.7	162.7±30.6	0.412	159.2±31.1
	Normal/High		28/2	25/2	0.915	53/4
	TGD (40–150 mg/dL)	Mean±SD	105.1±34.2	114.4±41.3	0.357	109.5±37.7
	Normal/High		26/4	22/5	0.60	48/9
	LDL (<130 mg/dL)	Mean±SD	97.07±30.66	102.47±30.0	0.505	99.62±30.21
	Normal/High		27/3	22/5	0.364	49/8
	HDL (35–85 mg/dL)		41.27±8.98	38.17±6.84	0.152	39.8±8.12
Histopathology	**Fibrosis stage**	I/II/III	14/11/5	11/14/2	0.856	25/25/7
	Activity grade	0/I/II/III	2/16/8/4	2/19/5/1	0.153	4/35/13/5

SD: standard deviation; BMI: body mass index (†Normal/overweight/obese=<25/25–29/≥30, respectively); CBC: complete blood count; Hb: hemoglobin; Plts: platelets; TLC: total leucocyte count; LBP: liver biochemical profile; ALT: alanine aminotransferase; AST: aspartate aminotransferase; Bil: bilirubin; TC: total cholesterol; TGD: triglycerides; LDL: low density lipoprotein; HDL: high density lipoprotein
Statistically significant p values are highlighted in bold.

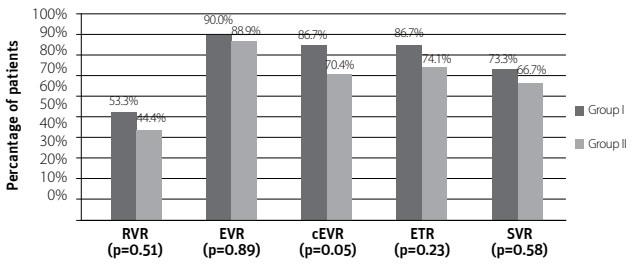

Figure 1. Virological responses in the two study groups.

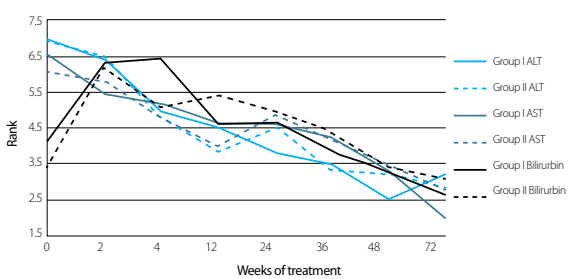

Figure 2. Monitored transaminases and bilirubin along the treatment course in the two study groups.

To identify the limiting factors influencing the viral response, correlations between various patients' data in relation to RVR, EVR, and SVR are shown in Table 2. RVR was significantly influenced by low viral load and high LDL (p=0.005 and 0.019, respectively). EVR was negatively influenced by smoking (p=0.001) and positively influenced by low viral load and high ALT (p=0.044 and 0.017 respectively), whereas SVR was significantly related to the fibrosis stage.

DISCUSSION

Statins are a group of drugs capable of inhibiting HMG-CoA reductase, thereby regulating cholesterol synthesis by competing with the authentic substrate (10). They interfere with the replication of HCV by various mechanisms. Firstly, HCV circulates in association with LDL-cholesterol (11), and the LDL-cholesterol receptor serves as the HCV receptor for its entry to hepatocytes (12,13). Secondly, HCV RNA replicates within hepatocytes in association with lipid droplets (3,14); therefore, blocking the synthesis of cholesterol by statins inhibits a mechanism favouring HCV survival. However, the response to IFN is more favorable in patients with higher LDL (15,16). Thirdly, statins inhibit mevalonate synthesis, which was modified later into geranylgeranyl and subsequently into farnesyl (8,17). Both lipidate most cellular proteins to become lipophilic; hence, the geranylgeranyl protein is formed by binding geranylgeranyl pyrophosphate to the host protein, enabling it to express their biological activities (18). This geranylgeranylated protein plays an important role in HCV replication (19). Moreover, cholesterol is critical to HCV replication. Thus, statins can inhibit HCV replication by inhibiting its synthesis (2,4,19). FLV inhibits HCV replication effectively in vitro (5,20) when used solely in the treatment of HCV patients at daily doses of 20–320 mg for 2–12 weeks (6). FLV might improve treatment outcomes in patients with genotype 1b and in patients with a high viral load when added to SOC therapy (21). This proposed triple therapy significantly increased the SVR rate (22). We compared the virological response between the triple therapy in group I (FLV, PEG-IFN, and ribavirin) and SOC therapy in group II. SVR was numerically higher, though not statistically significant, in group I than in group II (73.3% and 66.7%, respectively; p=0.601). Studies have demonstrated different results in this context. For instance, in their study on HCV genotype 1b patients in 2012, Kondo et al. (22) found a significantly higher SVR in the FLV arm than in the SOC arm (63.0% vs. 41.7%, respectively; p=0.04). In contrast, Milazzo et al. (23) found results similar to the current study, where a higher SVR was found in the FLV group (38%) than in the SOC group (13%), with no statistical significance (p=0.08). It should

Table 2. Correlation (Pearson's correlation) between patient demographics, pretreatment viral load, transaminases, lipid profiles, and histological parameters and their influence on viral response

		RVR			EVR			SVR		
Parameter		**Group I**	**Group II**	**Total**	**Group I**	**Group II**	**Total**	**Group I**	**Group II**	**Total**
Age (≤40 years/>40 years)		0.925	0.102	0.259	0.640	0.295	0.270	0.549	0.355	0.237
Smokers/non-smokers		0.708	0.653	0.918	**0.050**	**0.003**	**0.001**	0.466	0.288	0.969
BMI (Normal/Overweight/Obese)		0.944	0.953	0.879	0.728	0.129	0.181	0.764	0.714	0.703
Viral load (<800 000/≥800 000)		0.075	0.032	**0.005**	0.281	0.060	**0.044**	0.447	0.074	0.084
ALT (Normal/high)		0.560	0.066	0.419	0.105	0.094	**0.017**	0.251	0.160	0.852
AST (Normal/high)		0.825	0.431	0.620	0.679	1.00	0.767	0.251	0.541	0.583
Cholesterol	Absolute level	0.787	**0.019**	0.095	0.776	**0.045**	0.253	0.424	0.542	0.247
	Normal/high	0.183	0.876	0.291	0.640	0.620	0.486	0.549	0.641	0.429
Triglycerides	Absolute level	0.097	0.758	0.159	0.183	0.566	0.183	0.585	0.786	0.511
	Normal/high	0.237	0.239	0.081	0.299	0.502	0.220	0.549	0.556	0.370
HDL	Absolute level	0.876	0.248	0.503	0.121	0.890	0.248	0.214	0.654	0.333
	Normal/low	0.508	0.401	0.930	0.118	0.351	0.415	0.224	0.196	0.413
LDL	Absolute level	0.220	0.016	**0.013**	0.886	**0.020**	0.092	0.314	0.594	0.194
	Normal/high	0.093	0.082	**0.019**	0.559	0.401	0.304	0.453	0.416	0.237
Fibrosis	Stages I/II/III	0.567	0.543	0.409	0.937	1.000	0.948	**0.014**	0.811	**0.044**
	stages I–II/III)	0.529	0.876	0.729	0.432	0.620	0.735	**0.038**	0.749	**0.050**
Hepatitis	Grades 0/1/2/3	0.816	0.893	0.814	0.307	0.595	0.247	0.223	0.680	0.356
	grades 0–1/2–3	0.775	0.767	0.930	0.812	0.345	0.415	0.163	0.416	0.413

RVR: rapid virological response; EVR: early virological response; SVR: sustained virological response; vs: versus; BMI: body mass index; ALT: alanine aminotransferase; AST: aspartate aminotransferase; HDL: high density lipoprotein; LDL: low density lipoprotein

Statistically significant p values are highlighted in bold.

be noted that the latter study was performed on HCV/HIV co-infected patients.

We studied the various virological responses throughout the course of therapy. We found higher RVR, EVR, and ETR rates in the FLV group than in the SOC group (53.3%, 90%, and 86.7% vs. 44.4%, 88.9%, and 74.1%, respectively); however, this difference was statistically non-significant. This result was similar to the results of the study by Kondo et al. (22) in 2012 because they found no significantly higher rates of RVR, EVR, and ETR in the FLV group than n the SOC group. Milazzo et al. (23) found a significantly higher RVR on adding FLV to SOC, whereas EVR and ETR rates showed no significant differences between the two groups. Moreover, high LDL-C (≥86 mg/dL) was found to be a significant determinant to both EVR and SVR (15).

EVR per se, is a good predictor of SVR (15). In addition, classifying EVR into cEVR and dEVR has been of much concern in different clinical practice guidelines in terms of HCV therapy duration. For instance, EASL guidelines (24) recommended 48 weeks of therapy for patients achieving cEVR, regardless of HCV genotype and baseline viral load as well as the possibility of treating genotype 1 patients with dEVR for 72 weeks, which may also apply to other genotypes. This study draws special attention to the virological responses in terms of cEVR and dEVR, where we found a borderline significant increase in patients with cEVR in the FLV group compared with the SOC group (86.7% vs. 70.4%, respectively; p=0.05). Thus, adding FLV to SOC may be considered a synergistic adjuvant to anti-HCV treatment (24). In this study, FLV proved to be a safe adjuvant to SOC in HCV patients. The tolerability of the two treatment schedules (groups I and II) was comparable clinically. Regarding the laboratory results, only one patient in group I showed a significant rise of ALT by week 24, for which he continued treatment by SOC therapy alone. This was similar to previous studies documenting the safe use of statins in HCV-infected patients without the risk of hepatotoxicity (23,25-28). Another patient discontinued treatment at week 28 because of retroperitoneal infection that was drained surgically.

Different studies have focused on factors influencing the virological response. In this study, RVR was significantly influenced by low viral load and high LDL, whereas SVR was significantly influenced by the fibrosis stage. EVR was negatively influenced by smoking (p=0.001) and positively related to low viral load and high ALT. Milazzo et al. (23) found none of the patients' demographics or laboratory results to be correlated with SVR. Although Kondo et al. (22) found male gender, high Hb, and high TLC to be associated with SVR in FLV-treated patients, Harrison showed that low HDL and high LDL levels influenced SVR (29). The gender factor, in the current study, was biased because almost all of the enrolled subjects were males. This is attributed to the type of patients attending the outpatient clinic at ACMC, which is a construction company in Egypt. Most of the patients were middle-aged males (engineers, employees, drivers, and workers in the field of building and construction), and the only female patient was an engineer.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Endemic Medicine Department, Faculty of Medicine, Cairo University.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - .S.S.; Design - A.F.S.; Supervision - Z.A.S.; Resource - M.A.M.; Materials - H.A.G.; Data Collection and/or Processing - H.A.G.; Analysis and/or Interpretation - R.N.M.; Literature Search - M.A.M.; Writing - R.N.M., M.A.M.; Critical Reviews - A.F.S., Z.A.S.

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