Impact of Added Fluvastatin to Standard-of-Care Treatment on Sustained Virological Response in Naïve Chronic Hepatitis C Patients Infected with Genotypes 1 and 3

Tanja Selic Kurincic^a Gorazd Lesnicar^a Mario Poljak^b Jelka Meglic Volkar^c
Mojca Rajter^c Janja Prah^c Zvonko Baklan^d Tadeja Kotar^c Mojca Maticic^c

^aDepartment of Infectious Diseases and Febrile Conditions, General Hospital Celje, Celje, ^bInstitute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, and ^cClinic for Infectious Diseases and Febrile Illnesses, University Medical Centre Ljubljana, Ljubljana, and ^dDepartment of Infectious Diseases and Febrile Illnesses, University Clinical Centre Maribor, Maribor, Slovenia

Key Words

Chronic hepatitis C · Pegylated interferon- α · Ribavirin · Fluvastatin · Sustained virological response

Abstract

Objectives: The combination of pegylated interferon- α and ribavirin is a standard-of-care (SOC) treatment for chronic hepatitis C (CHC), and it achieves a sustained virological response (SVR) in 41–52% of genotype 1 and in 73–79% of genotype 3 patients. In a few clinical trials, the combination of fluvastatin and SOC increased the SVR in genotype 1 patients. **Methods:** This prospective study enrolled 179 naïve CHC patients. In the fluvastatin group patients received the combination of SOC and fluvastatin 80 mg daily; historical controls matching the study group in genotype, age and gender were treated with the SOC treatment only. **Results:** On-treatment viral responses as well as the SVR did not differ significantly between the two groups, except for the genotype 1 patients with a high viral load presenting a significantly higher SVR rate in the fluvastatin group (75%) compared to the control group (41%; $p = 0.024$). Multivariate logistic regression identified hepatitis C virus (HCV) genotype 3 infection ($p < 0.001$), age ≤ 40 years ($p < 0.001$), liver steato-

sis $< 5\%$ ($p < 0.01$) and low viral load ($p < 0.001$) as independent predictors of an SVR. **Conclusion:** A combination of fluvastatin and SOC significantly improved the SVR in naïve CHC patients infected with HCV genotype 1 and high viral load, but it did not improve the SVR in patients infected with HCV genotype 3.

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Introduction

In Central Europe the prevalence of hepatitis C virus (HCV) infection is intermediate, ranging from 0.2–1.2%, with intravenous drug use being the primary mode of transmission during the last years [1, 2]. In Slovenia, which has a population of 2 million inhabitants, the prevalence of HCV infection is estimated to be below 1%, with a predominance of HCV genotype 1 (56%), followed by genotype 3 (37.8%), genotype 2 (5%) and genotype 4 (1.2%) [3, 4].

For the last 10 years, the combination of pegylated interferon- α (PEG-IFN α) and ribavirin (RBV) has presented a standard-of-care (SOC) treatment for chronic hepatitis C (CHC) [5]. Patients who achieve a sustained

virological response (SVR) are considered cured in more than 99% of the cases according to long-term follow-up studies [6, 7]. In pivotal clinical studies, an SVR was achieved in 41–52% of genotype 1 patients and in 73–82% of genotypes 2 and 3 patients treated with a SOC treatment [8–10]. In other clinical trials, genotype 1 patients achieved an SVR in 47–50% [11, 12], and those infected with genotype 3 in 69–79% [13, 14]. The most potent pretreatment factors for an SVR were viral genotype, baseline serum viral load, age, gender, BMI, stage of liver fibrosis and recently found genetic polymorphisms for interleukin 28B located on chromosome 19 [5, 15–17].

In vitro studies have shown that elements of cholesterol-biosynthetic pathways play a critical role in HCV replication, especially geranylgeranyl which is required for HCV replication. It has been demonstrated that statins (3-hydroxyl-3-methylglutaryl-coenzyme A reductase inhibitors) disrupt HCV-RNA replication in cultured hepatoma cells [18, 19]. Fluvastatin showed the strongest inhibition on viral replication, and in combination with interferon it had a synergistic inhibitory effect on HCV replication [20].

The aim of the present study was to investigate the impact of adding fluvastatin to SOC treatment on the SVR in a cohort of Slovene patients infected with HCV genotypes 1 and 3, and to determine how safe fluvastatin is for patients with CHC.

Patients and Methods

Study Design

This prospective, open-labeled, historically controlled study enrolled naïve intent-to-treat patients treated for CHC genotypes 1 and 3 according to the 2007 Slovene national consensus guidelines [21]. From September 2009 to February 2011, all of the eligible patients who agreed to participate in the study and who had provided informed consent received fluvastatin in combination with SOC treatment. All of the patients presented with baseline viremia detected by polymerase chain reaction determined by automated COBAS AmpliPrep/COBAS AMPLICOR HCV Test (Roche Diagnostic Systems) with a limit of detection of 30 IU/ml HCV-RNA, carried out at the national reference laboratory. Baseline patient characteristics were evaluated including the viral load, with a high viral load presenting >400,000 IU/ml. Pretreatment liver biopsy was performed in all patients except in those with contraindications. Histological diagnosis was performed according to METAVIR scoring system with the fibrosis stage ranging from 0 to 4 [22].

Patients with the following were excluded: decompensated cirrhosis, coinfection with HIV or HBV, any other cause of liver disease, leucocyte count <3,000/mm³, platelet count <75,000/mm³, hemoglobin <13 g/dl for men and <12 g/dl for women, uncontrolled depression, untreated thyroid disease and autoimmune diseases, clinically

significant cardiovascular diseases, malignant neoplastic diseases, previous therapy with statins, and poorly controlled diabetes.

Eligible patients in the study group were treated with a combination of a weight-based dose of RBV 15 mg/kg body weight per day plus either PEG IFN α -2a 180 μ g or PEG IFN α -2b 1.5 μ g/kg once weekly subcutaneously since no conclusive evidence showing a preference for one of the two PEG-IFN α had been reported [5, 23]. According to the viral genotype, baseline HCV-RNA and on-treatment virological response, the treatment duration was 24–72 weeks for genotype 1 and 24 weeks for genotype 3. All patients were additionally treated with fluvastatin 80 mg daily.

The historical control group consisted of all naïve patients with CHC genotypes 1 and 3 who completed treatment and follow-up; they were recruited from the national registry of treated patients and matched the study group in genotype, age and gender. Patients in the control group were treated with SOC treatment according to the same regime as the studied group regarding the treatment optimization (virological response-guided therapy, weight-based dose of RBV and aggressive management of side effects) which is in line with the Slovenian national guidelines [21].

Complete blood count and liver function tests were performed on a 2-week basis until week 8 of treatment and thereafter monthly until the end of treatment as well as at weeks 12 and 24 after cessation of treatment. HCV-RNA concentrations were determined at baseline; weeks 4, 12 and 24; at the end of treatment, and 24 weeks after cessation of treatment. In the fluvastatin group, the creatine kinase level was checked during the treatment.

The study was approved by The National Medical Ethics Committee of the Republic of Slovenia according to the Declaration of Helsinki and in compliance with the ICH/GCP requirements of good clinical practice and all the applicable regulations of the Republic of Slovenia.

Statistical Analysis

Due to the case-control design of the study, only the patients that completed treatment of CHC and a 24-week follow-up period were analyzed in both the study and the control groups. Firstly, the matching of both groups regarding significant SVR predictors was tested using the Mantel-Haenszel test for 2 $\times$ 2 $\times$ 2 comparisons, the likelihood ratio test for both groups per each specified stratum for categorical variables, and the Kruskal-Wallis test (both groups with respect to genotype and type of therapy) or t/Mann-Whitney U test for both groups per stratum [considering (non)normality of data distribution]. Analysis of the primary outcome, i.e. virological response according to genotype, viral load, pathohistological liver changes and mode of therapy, was performed using the likelihood ratio test. Statistical significance was set at $p < 0.05$.

Results

The study enrolled 179 naïve CHC genotypes 1 and 3 Caucasian patients: 81 treated with SOC treatment and fluvastatin, and 98 historical controls treated with SOC treatment only. In the study group, 17 patients discontinued treatment prematurely and were excluded from further analysis (fig. 1). Table 1 shows the baseline patient characteristics of the two groups.

Fig. 1. Trial profile.

Response to Therapy

The overall SVR was 89% in the study group and 79.6% in the control group ($p = 0.12$). Since the study was designed in a case-control manner, a preliminary comparison of the main SVR predictor balance between the two groups was performed using bivariate testing of the following: HCV genotype, low/high viral load ($\leq 400,000$ IU/ml/ $>400,000$ IU/ml), low/high BMI (≤ 30 / >30), low/high age (≤ 40 years/ >40 years), baseline low-density lipoprotein and baseline triglycerides. No significant overall difference was found ($\chi^2 = 2.5$; $p = 0.114$). However, a significant difference between the two groups was established in viral load with the fluvastatin group presenting a higher load, controlled for genotype (Mantel-Haenszel test: OR = 2.32, 95% CI: 1.17–4.59, $p = 0.023$). Kruskal-Wallis tests of absolute viral load (controlled for genotype) also showed a significant difference ($p = 0.01$), suggesting that groups do differ both in proportion of low/high viral load as well as in the absolute viral load. The results imply that the viral load should be considered as a possible confounder.

To further examine the possible confounders, data on SVR predictors were compared in both patient groups by the following four strata: (1) low viral load/genotype 1, (2) high viral load/genotype 1, (3) low viral load/genotype 3 and (4) high viral load/genotype 3. Except for the imbalance in higher triglyceride levels of the control group in

strata 3, no significant differences were found between the two groups with respect to any of the compared variables (age, BMI, liver fibrosis, baseline low-density lipoprotein and baseline triglyceride levels) in any of the four strata.

The rapid (RVR), early (EVR) and end-of-treatment (ETR) virological responses in the fluvastatin group genotype 1 were 35, 92 and 85%, respectively, while in the control group they were 42, 93 and 87%, respectively. In genotype 3 patients, RVR, EVR and ETR were 89, 100 and 100%, respectively, compared to 92, 100 and 98% in the control group, respectively. RVR, EVR and ETR did not differ significantly between the two groups (fig. 2). In the fluvastatin group, genotype 1 patients achieved an SVR in 81% of the cases compared to 64% in the control group ($p = 0.138$). In genotype 3 patients, the SVR was 95% in the fluvastatin group versus 92% in the control group ($p = 0.661$).

Data on the SVRs of the study group were tested unconditioned on HCV genotype and viral load using the χ^2 test. No significant overall difference was found ($\chi^2 = 2.5$; $p = 0.114$). Subsequently, data were tested separately by strata corresponding to the strata 1–4 with respect to the following virological responses: RVR, EVR, ETR and SVR. In the majority of subsets, virological responses did not differ significantly, except for the SVR among genotype 1 patients presenting a high viral load. In this subset,

Table 1. Baseline patient characteristics of the fluvastatin (n = 64) and the control (n = 98) groups

	All patients (n = 162)	Genotype 1		Genotype 3	
		fluvastatin (n = 26)	controls (n = 45)	fluvastatin (n = 38)	controls (n = 53)
Males	104 (64)	19 (73)	26 (58)	26 (68)	33 (62)
Age, years	35.1±9 [33]	35.2±9 [32]	39.6±11.2 [35]	32.8±4.9 [33]	32.8±7.9 [32]
≤40	128 (79)	21 (81)	27 (60)	35 (92)	45 (85)
>40	34 (21)	5 (19)	18 (40)	3 (8)	8 (15)
Risk factors					
Intravenous drug use	124 (76)	17 (65)	25 (55)	36 (94)	46 (87)
Transfusion	14 (9)	3 (12)	8 (18)	1 (3)	2 (4)
Other or unknown	24 (15)	6 (23)	12 (27)	1 (3)	5 (9)
BMI					
≤30	154 (95)	24 (92)	42 (93)	36 (94)	52 (98)
>30	8 (5)	2 (8)	3 (7)	2 (6)	1 (2)
HCV-RNA, IU/ml					
≤400,000	62 (38)	6 (23)	23 (51)	11 (29)	22 (42)
>400,000	100 (62)	20 (77)	22 (49)	27 (71)	31 (58)
Stage of liver fibrosis ^a					
0–1	83 (51)	15 (57)	19 (42)	20 (53)	29 (55)
2	43 (27)	5 (19)	10 (22)	14 (37)	14 (26)
3–4	14 (9)	3 (12)	8 (18)	0 (0)	3 (6)
Missing data	22 (13)	3 (12)	8 (18)	4 (10)	7 (13)
Steatosis					
<5%	105 (65)	18 (69)	29 (64)	23 (61)	35 (66)
>5%	35 (22)	5 (19)	8 (18)	11 (29)	11 (21)
Missing data	22 (13)	3 (12)	8 (18)	4 (10)	7 (13)
Liver enzymes, IU/l					
ALT	1.7±1.4 [1.3]	1.7±1.6 [1.3]	1.6±1.5 [0.9]	1.7±1.2 [1.4]	1.8±1.4 [1.5]
AST	1±0.7 [0.9]	1±0.7 [0.8]	1±0.9 [0.7]	1.1±0.6 [0.9]	1±0.6 [0.9]
GGT	0.9±1 [0.6]	1±1 [0.9]	0.9±0.8 [0.6]	1±0.9 [0.6]	0.8±1.2 [0.6]
Baseline glucose, mmol/l	5±1 [5]	5.3±2.1 [5]	5±0.5 [4.9]	5±0.6 [5]	4.9±0.6 [4.9]
Baseline serum lipids, mmol/l					
Total cholesterol	4.4±1 [4.4]	4.5±0.9 [4.4]	4.7±0.9 [4.8]	4.2±1.1 [3.9]	4.2±0.9 [4.3]
Triglycerides	1.3±0.7 [1.1]	1.2±0.6 [1.15]	1.3±0.4 [1.2]	1.2±0.8 [1.1]	1.4±0.9 [1.2]
HDL-cholesterol	1.4±0.4 [1.3]	1.4±0.3 [1.3]	1.5±0.5 [1.4]	1.3±0.4 [1.2]	1.3±0.3 [1.2]
LDL-cholesterol	2.4±0.8 [2.4]	2.7±0.7 [2.7]	2.5±0.9 [2.5]	2.3±0.9 [2.2]	2.3±0.7 [2.2]
Missing data	26 (16)	0 (0)	8 (18)	2 (5)	16 (30)

Results are expressed as n (%) or means ± SD with medians in square brackets. HCV-RNA represents the baseline viral load. ALT = Alanine transaminase; AST = aspartate transaminase; GGT = γ -glutamyl transaminase; HDL = high-density lipoprotein; LDL = low-density lipoprotein. ^a Liver histology was graded according to METAVIR score.

an SVR was achieved in 15 of 20 patients (75%) in the fluvastatin group and in 9 of 22 patients (41%) in the control group (likelihood ratio test: 5.104, $p = 0.024$).

In order to investigate the predictive factors of an SVR, we analyzed the viral and the pretreatment host factors. Overall, the proportion of patients achieving an SVR was higher in HCV genotype 3 infection versus genotype 1 infection (93 vs. 70%, respectively), higher among patients receiving SOC treatment with added fluvastatin versus patients receiving SOC treatment only (89 vs. 80%, respec-

tively), higher in case of liver steatosis <5% versus steatosis ≥5% (89 vs. 69%, respectively), higher in case of liver fibrosis METAVIR stages 0–1 versus METAVIR stages 2–4 (87 vs. 79%, respectively), considerably higher among younger patients (≤40 years) versus older ones (95 vs. 41%, respectively), higher in BMI ≤30 versus BMI >30 (84 vs. 75%, respectively), and considerably higher among patients with a baseline viral load ≤400,000 IU/ml versus patients with a baseline viral load >400,000 IU/ml (94 vs. 77%, respectively). The differences reached significance

Fig. 2. Comparison of virological response rates between the fluvastatin and the control groups in patients infected with HCV genotypes 1 (a) and 3 (b).

Table 2. Results of bivariate and multivariate logistic regression in predicting failure in reaching the SVR

Predictor	Bivariate			Multivariate		
	OR	95% CI	p	OR	95% CI	p
Genotype (1)	0.2	0.1–0.4	<0.001	0.1	0–0.4	<0.001
Group (control)	0.5	0.2–1.2	0.12	0.6	0.1–2.6	0.46
Age (>40)	0.04	0.02–0.11	<0.001	0.03	0.01–0.14	<0.001
Stage of fibrosis (0–1)	1.7	0.7–4.3	0.22	1.2	0.3–4.9	0.75
BMI (≤30)	1.7	0.3–9	0.52	0.6	0–25.9	0.81
Steatosis (<5%)	3.6	1.4–9	0.01	6.4	1.5–28.3	0.01
HCV-RNA (≤400,000)	4.3	1.4–13.2	0.01	22.6	3–171.5	<0.001

HCV-RNA represents the baseline viral load. The reference category of each predictor is indicated in parentheses.

using a multivariate logistic regression in four variables: HCV genotype 3 infection, patients ≤40 years old, steatosis <5% and baseline viral load ≤400,000 IU/ml, all being associated with higher odds of an SVR (table 2).

Safety and Tolerability

In the fluvastatin group, RBV dose reduction due to anemia was necessary in 8 of 64 patients (12.5%) compared to 4 of 98 (4%) in the control group ($p = 0.06$). Erythropoietin was administered in 4 of 64 patients (6%)

in the fluvastatin group versus 3 of 98 (3%) in the control group ($p = 0.36$). Granulocyte colony-stimulating factor was prescribed in 1 patient out of 64 (1.6%) in the fluvastatin group versus 4 of 98 (4%) in the control group ($p = 0.42$). Most patients had mild or moderate psychiatric adverse events, although 1 patient in each group needed hospitalization at a psychiatric medical hospital. Hypothyroidism was seen in 2 of 64 patients (3%) in the fluvastatin group compared to 2 of 98 (2%) in the control group ($p = 0.69$), while hyperthyroidism presented in 3 of

64 (4.7%) of the fluvastatin group versus 2 of 98 (2%) in the control group ($p = 0.39$). One patient in the fluvastatin group (1.6%), who had also received other hepatotoxic drugs, discontinued treatment 5 months after the introduction of treatment due to an increase in γ -glutamyl transferase level ($p = 0.40$). No significant differences in side effects were detected between the two groups.

Discussion

This is the first report on the efficacy of optimized SOC treatment with added fluvastatin in HCV genotype 3-infected patients, as well as the first report on HCV genotype 1 monoinfected patients treated with a fluvastatin dose of 80 mg daily. Eligible patients received a maximal daily dose of fluvastatin approved by the FDA since there are no published data on the correlation between the oral dose of statins and the level of statins in human hepatocytes. In the last 4 years, only a few studies have been published evaluating the clinical effect of fluvastatin on viral response; however, the results have been controversial. In the first clinical trial, Bader et al. [24] reported that monotherapy with fluvastatin showed variable and often short-lived suppressive effects on viral load. In a pilot study, Sezaki et al. [25] demonstrated that the addition of fluvastatin 20 mg daily to SOC treatment might increase the SVR in patients infected with HCV genotype 1b and a high viral load. Recently, Georgescu et al. [26] and Kondo et al. [27] reported that the addition of fluvastatin 20 mg daily to SOC treatment significantly improved the SVR in patients infected with HCV genotype 1b. However, Milazzo et al. [28] reported that the addition of fluvastatin 80 mg daily to SOC treatment did not significantly improve the SVR among HIV/HCV-coinfected patients, but significantly improved RVR. According to our knowledge, no studies have been performed regarding the use of fluvastatin in genotype 3 patients.

In the present study, an SVR was achieved in more than 90% of genotype 3 patients with or without fluvastatin added to the optimized SOC treatment. In the previous studies using various regimens of SOC treatment optimization, the SVR was shown to be 68–74% [13, 29]. Overall, the combination of fluvastatin and optimized SOC treatment showed no significant improvement in the SVR among genotype 3 patients.

In genotype 1 patients, an SVR was achieved in 81% in the fluvastatin group, which is much higher compared to 37–50% in other clinical studies [12, 29]. However, compared to 64% in the control group, the difference was not

significant. Interestingly, further analysis of the subgroups showed that the addition of fluvastatin to the optimized SOC treatment significantly improved the SVR in genotype 1 patients and high viral load ($>400,000$ IU/ml), which is in accordance with published studies [26, 27].

One of the reasons for high SVR in our study and control patients was the study design since only the patients who completed treatment and follow-up were analyzed. In addition, favorable pretreatment factors, including a high rate of patients with genotype 3 infection, age ≤ 40 years (in 79%), BMI ≤ 30 (in $>95\%$), liver steatosis $<5\%$ (in 65%) and liver fibrosis METAVIR stages 0–1 (in 51%), also contributed to the results, which is in agreement with the relevant studies [5, 14, 29].

Another reason for the high SVR rate was probably the optimization of the SOC treatment in both groups, including a weight-based dose of RBV in genotypes 1 and 3, viral response-guided treatment duration according to RVR and EVR, and the aggressive management of side effects [5, 30, 31]. All of the included drug users were treated according to the Slovenian national consensus guidelines for the management of HCV infection in drug users [21]. Regular monitoring and follow-up visits of the patients enabled optimal treatment adherence to both PEG-IFN plus RBV and prescription of erythropoietin, granulocyte colony-stimulating factor and antidepressants to avoid premature treatment discontinuation due to side effects.

Discontinuation of fluvastatin therapy as a result of severe hepatotoxicity was needed in 1 patient only (1.6%). According to the National Lipid Association Statin Safety Task Force, patients with chronic liver disease may safely receive statin therapy [32]. Khorashadi et al. [33] reported that statin use did not increase severe hepatotoxicity in patients with HCV infection. In the present study, fluvastatin use in patients with CHC proved to be safe.

We are fully aware of some study limitations, particularly the design of a nonrandomized trial for the use of fluvastatin and a small number of patients after performing stratification and logistic regression. As a general rule, an adequate sample size for logistic regression should comprise at least 10 events per included independent variable [34]. Therefore, three predictors at most were included in the present analysis to obtain valid results. However, as this is not in accordance with the general rule, this should be borne in mind when generalizing the results to the population. Due to a relatively small total number of known CHC patients in Slovenia, a historical-control study design was performed as it was also used in other pivotal clinical trials [12, 14].

In conclusion, the present study contributes new data on the SVR in patients with CHC treated with the optimized SOC treatment plus fluvastatin. Moreover, addition of fluvastatin to SOC treatment might be an advantageous therapeutic option for the treatment of genotype 1 patients and high baseline viral load. It should also be noted that despite new treatment options for CHC, the combination of statins with protease inhibitors may result in a more potent antiviral activity, and this combina-

tion may also delay or prevent the development of resistance to protease inhibitors [35]. Moreover, fluvastatin is not contraindicated with protease inhibitors because it is mainly metabolized by cytochrome P450 2C9 and not by the cytochrome P450 3A isoenzyme, which is strongly inhibited by boceprevir and telaprevir [36, 37]. As for the genotype 3 patients, according to previously reported SVR rates, further clinical research on the combination of SOC treatment and fluvastatin is warranted.

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