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A randomized controlled trial adding fluvastatin to peginterferon and ribavirin for naïve genotype 1 hepatitis C patients

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SUMMARY. Fluvastatin or simvastatin has demonstrable antiviral activity against hepatitis C virus (HCV) as monotherapy. The safety and efficacy of adding fluvastatin or simvastatin to peginterferon/ribavirin for 48 weeks was tested in HCV genotype 1 naïve-to-treatment veterans. Thirty-seven naïve-to-treatment genotype 1 HCV patients were randomized to either a control group ($n = 20$) to receive peginterferon alfa plus ribavirin or an experimental group ($n = 18$) to similarly receive peginterferon alfa plus ribavirin as well as fluvastatin 20 mg/day. In addition, seven patients who presented for HCV treatment already were on simvastatin and could not be withdrawn. These simvastatin users were not randomized but were entered into a concurrent prospective pilot arm. There were no unique safety issues with fluvastatin or simvastatin when these drugs were given with peginterferon/ribavirin for 48 weeks. Thirteen of 25 statin patients achieved sustained viral response (SVR), while 5 of 20 control patients achieved SVR. Analysis of SVR by intention-to-treat showed $P = 0.078$. In this phase 2 study, there were no safety issues with the addition of fluvastatin or simvastatin to peginterferon and ribavirin for 48 weeks. There was a trend towards improvement in SVR when fluvastatin or simvastatin was administered with peginterferon/ribavirin. The size of the groups did not reach the prestudy size thought needed to show significant difference (type II error). These results support the significant results of two other larger randomized controlled trials reported using the same dose of fluvastatin in naïve-to-treatment genotype 1 HCV patients.

Keywords: fluvastatin, hepatitis C, peginterferon alfa, ribavirin, simvastatin.

INTRODUCTION

Brown and Goldstein won the Nobel Prize in 1985 for their work on isolating and characterizing low-density lipoprotein (LDL). Brown and Goldstein also were the first to suggest that a statin, lovastatin, possessed an anti-HCV effect in a hepatitis C virus (HCV) replicon culture system [1]. Ikeda *et al.* [2] then performed an *in vitro* dose *vs* antiviral effect for all available statins. They reported that fluvastatin had the strongest anti-HCV activity.

Under a phase 1 Food and Drug Administration (FDA), USA licence, we previously were able to demonstrate an antiviral dose for fluvastatin in humans infected with chronic hepatitis C virus [3]. The FDA-approved doses of fluvastatin for use against hypercholesterolaemia are 20–80 mg/day. As Ikeda *et al.* had suggested that higher concentrations of statin *in vitro* possessed more anti-HCV activity, we tested doses up to 4 × the upper limit approved by the FDA for hypercholesterolaemia (i.e. 320 mg/day). Paradoxically, we determined that the lowest approved dose of fluvastatin, 20 mg/day, was the most active anti-HCV dose in humans when used as monotherapy. The anti-HCV effect with fluvastatin monotherapy is modest with decrements of HCV RNA in the range of 0.5–1.0 logs. It usually lasts a few days to a few weeks, although one patient experienced a 3-log HCV RNA drop 1 year later [3]. For comparison,

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FLV, fluvastatin; HCV, hepatitis C virus; ITT, intention-to-treat.; LDL, low-density lipoprotein; RBV, ribavirin; SIM, simvastatin; SVR, sustained viral response.

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this direct antiviral effect of fluvastatin monotherapy is significantly stronger and longer-lasting than the direct antiviral effect of ribavirin used alone [4,5].

Our phase 1 FDA monotherapy trials of statins in patients with chronic HCV did not show safety problems. Specifically, we did not note any symptomatic or laboratory evidence of myopathy, although our numbers were small (n = 50). Unexpectedly, we saw uniform improvement in abnormal alanine aminotransferase (ALT) values that often normalized and lasted the duration of the statin use [3,6].

The primary purpose of this phase 2 FDA-licensed trial was to examine safety issues occurring when fluvastatin was combined with peginterferon/ribavirin over 48 weeks. Phase 2 trials are small so as to limit exposure of subjects and not sized to prove efficacy as in the case of phase 3 trials. The FDA does not require randomization of subjects for phase 2 trials, but reviewers permit it. We randomized the cohort to better compare the development of safety issues. A secondary prestudy goal was to evaluate efficacy by intention-to-treat with the realization that our enrolment may not achieve an adequate size to reduce type 2 error below the typically accepted level of 20%.

METHODS

Study design

The entire study took place within the gastrointestinal section of the Oklahoma City Veteran's Administration Medical Center. Patients were enrolled from 20 July 2007 until 20 October 2010. All genotype 1 HCV patients were eligible for entry if they were between the ages 18 and 70 and had never been treated with interferon or peginterferon before. Patients were excluded for the following reasons: (i) decompensated cirrhosis, (ii) severe cardiopulmonary disease, (iii) chronic renal insufficiency (GFR < 50 mL/min), (iv) HIV positivity, (v) hepatitis B surface antigen positivity and/or (vi) significant unexplained chronic muscle pain. Figure 1 shows the flow of patients through the study. Thirty-eight patients were not taking a statin upon enrolment and were randomized to either the control arm (n = 20) treated with peginterferon alfa-2a plus weight-based ribavirin or the experimental arm (n = 18) treated with the same regimen plus 20 mg/day fluvastatin. In addition, seven patients presented for HCV treatment already on simvastatin for their hypercholesterolaemia and could not be exposed to withdrawal of statin with

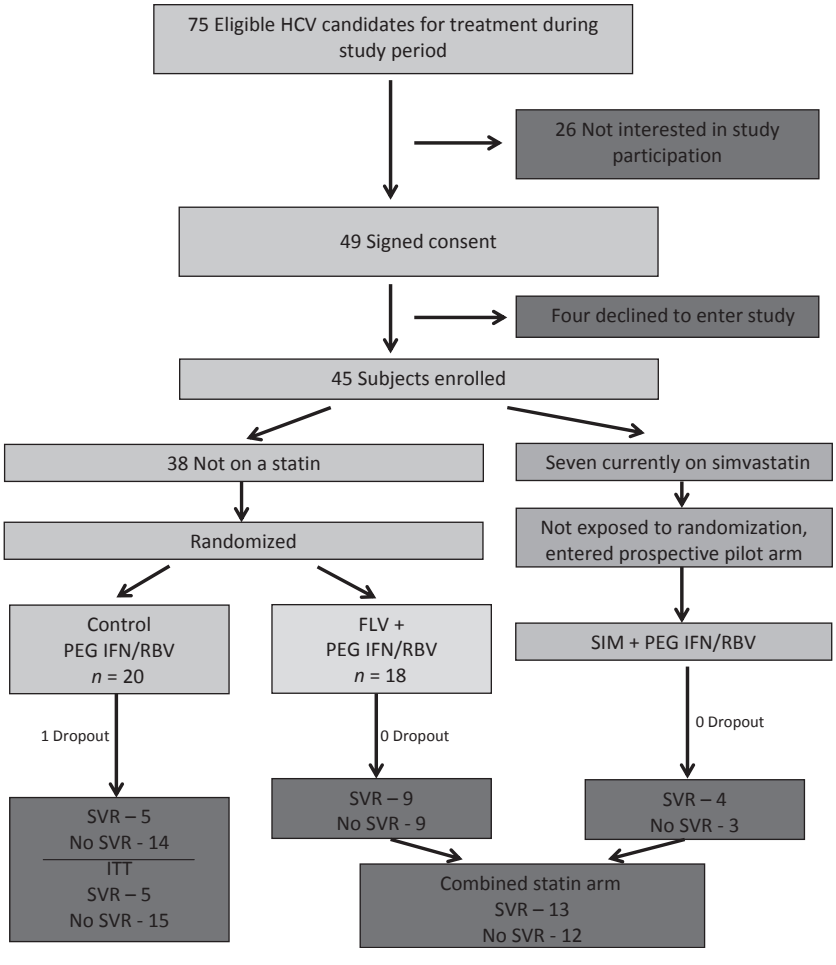

Fig. 1 Flow chart of the study. PEG IFN, peginterferon; RBV, ribavirin; FLV, fluvastatin; SIM, simvastatin; SVR, sustained viral remission; ITT, intention-to-treat.

randomization. The dose of simvastatin ranged from 10 to 80 mg/day. These simvastatin users were entered into a concurrent prospective pilot arm and analysed together with the fluvastatin arm as the statin group ($n = 25$).

Laboratory measurements

The endpoint for efficacy was sustained viral response (SVR) measured as an undetectable HCV RNA 24 weeks after the end of treatment. All HCV RNA samples were analysed using an in-house real-time Roche Cobas® PCR measurement machine that was leased and periodically upgraded for the latest technical advancements in measuring HCV RNA. Over the time period of the study, the lower limit of signal detection for HCV RNA at our institution was 20 IU/mL. As placebos do not influence HCV RNA levels in chronic hepatitis C patients, medicines were administered in an open-label format.

In addition to standard monitoring of patients on peginterferon and ribavirin, creatine kinase levels in all patients were measured periodically throughout the study. Reporting of side effects followed the National Cancer Institute's Criteria for Adverse Events, version 3.0 (2003), located at http://ctep.cancer.gov/reporting/ctc.html.

Statistical analysis

Results were expressed as means ± SD. Differences between groups were analysed by Student's *t*-test for continuous measures and Fisher's exact test for categorical measures. An intention-to-treat analysis for SVR results was carried out. A nominal significance level of 5% was assumed for the two-tailed tests. The *a priori* sample size of 40 for each group was determined to allow for 80% power to detect a minimal difference of 35% in SVR between the groups with maximum allowable type I error of 5%. SAS computer statistical package, version 9.1 (SAS Institute Inc, Cary, NC, USA), was used to analyse the data.

Oversight and approvals

This was an investigator-initiated trial. The principal investigator responsible for the trial was TB. The FDA Investigational New Drug licence number was 75605. The clinical trial registration number was NCT00487318. Institutional review board study approval was under the auspices of The University of Oklahoma Health Sciences Center Institutional Review Board and the VA Research and Development Committee, Oklahoma City, OK.

RESULTS

The baseline characteristics of the statin and control groups are given in Table 1. The 44 subjects were all male veterans, ranging in age from 34 to 65 years.

Safety

The primary purpose of this phase 2 trial was to observe unfamiliar side effects when fluvastatin was added to peginterferon/ribavirin for 48 weeks. There were no unique side effects noted beyond the usual adverse effects with the combination of peginterferon and ribavirin. Creatine kinase levels were checked an average of 3× per patient throughout the study. Enquiry about symptoms of unexplained muscle pain was monitored for the possibility of statin-induced myopathy. No patient reported an episode of unexplained muscle pain. The highest multiple of the upper limit of normal for creatine kinase that occurred in the fluvastatin, simvastatin and control arms was 2.5, 1.4 and

Table 1 Clinical and demographic profile of the patients' outcome

	Statin ($n = 25$)	Control ($n = 20$)	*P* value
Age (years)	54 ± 6	54 ± 5	0.99
Race: # white	20 (80%)	15 (75%)	0.73
Weight (lbs)	215 ± 44	220 ± 35	0.68
Diabetes mellitus	4 (16%)	3 (15%)	0.99
Platelet count ($\times 10^3$)	213 ± 48	197 ± 46	0.25
AST (IU/L)	50 ± 31	56 ± 31	0.51
HCV RNA (IU/mL)	3721236 ± 3187349	3852940 ± 3760296	0.90
LOG HCV RNA (IU/mL)	6.3 ± 0.6	6.3 ± 0.6	0.90
LDL cholesterol (mg/dL)	95 ± 32	102 ± 28	0.46
Total cholesterol (mg/dL)	154 ± 35	156 ± 27	0.82
Outcome SVR	13 (52%)	5 (25%)	0.078

AST, aspartate aminotransferase; HCV, hepatitis C virus; LDL, low-density lipoprotein ; SVR, sustained viral response.

1.7, respectively. Perhaps the best overall safety assessment for the study was the very low drop-out rate in any arm for any reason. None of the 25 statin group patients discontinued treatment, while only one of the 20 controls did.

Efficacy

Figure 1 and Table 1 list the outcome of efficacy when measured with intention-to-treat. Thirteen of 25 statin patients achieved SVR, while five of 20 controls did ($P = 0.078$).

There were seven African American men: two in the fluvastatin arm, two in the simvastatin arm and three in the control arm. Only one African American achieved SVR while taking 80 mg/day simvastatin.

DISCUSSION

Safety

The primary purpose of the trial was to evaluate the safety issues involved when fluvastatin or simvastatin was added to peginterferon/ribavirin for 48 weeks. When we combined either fluvastatin or simvastatin prospectively with peginterferon/ribavirin in 25 patients for 48 weeks, we did not observe any unique difficulty and no patient discontinued therapy. Other groups who have combined 20 mg/day of fluvastatin with peginterferon/ribavirin in larger randomized control trials (RCTs) (noted later) also have failed to report any unique side effects or the occurrence of myopathy with the use of fluvastatin. The worldwide prospective RCT experience with 20 mg/day fluvastatin when combined with peginterferon/ribavirin and used against HCV for 48-week therapy now totals 181 patients for 8 688 weeks of drug exposure without incident. The latter fluvastatin total does not include our seven simvastatin patients or nonrandomized prospective studies of fluvastatin/peginterferon/ribavirin [7].

Efficacy

When fluvastatin or simvastatin was added to peginterferon/ribavirin, 13 of 25 (52%) obtained sustained viral response (SVR), whereas in the control group using peginterferon/ribavirin, 5 of 20 (25%) reached SVR ($P = 0.078$). This indicates a strong trend favouring the addition of fluvastatin. We did not reach our enrolment goal of 80 patients that was based on the results of a retrospective study of patients who by chance took a statin along with peginterferon and ribavirin [8]. Thus, it is likely that an insufficient sample was accumulated. Enrolling patients became difficult when the promise of direct antiviral agents became a reality. Notably, maintaining the observed proportion of SVR in each group and artificially increasing the total sample size to 80 gave $P = 0.021$.

As with any RCT, a positive statistical effect favouring the intervention can be disguised by poor performance of the control group. Our current control group achieved a 25% SVR rate. This is identical to our previous retrospective report of naïve-to-treatment genotype 1 patients not on a statin of 25% (16/65) [8]. The national VA database for this same classification of genotype 1 patients ($n = 20\,477$) has been reported to have an SVR rate of 26% [9]. Thus, our control group performed the same as our own published historical group or the national VA database.

The 52% SVR rate for the statin group in the current report compares similarly to our retrospective SVR report of 55%. Throughout the time period encompassed by both the retrospective database and prospective trial, the statin used almost exclusively for hypercholesterolaemia in the VA system was simvastatin. Accordingly, 20 of 25 HCV patients in the retrospective statin report were taking simvastatin [8].

In any case, our results serve to support the results of two other RCTs of fluvastatin published that have tested the addition of our discovered dose of 20 mg/day of fluvastatin to peginterferon/ribavirin. Georgescu *et al.* gave fluvastatin 20 mg/day combined with peginterferon/ribavirin in an RCT to 104 naïve-to-treatment genotype 1 patients and compared the outcome with 105 control patients. The SVR rates were 63.5% and 49.5% ($P = 0.05$), respectively. When the 50 patients with metabolic syndrome (as defined by National Cholesterol Education Program Adult Treatment Panel III criteria) were subtracted from each arm in a *post hoc* analysis, the SVR rates were 74.4% and 58.4%, respectively ($P = 0.049$) [10].

The second trial reported by Kondo *et al.* [11] also used 20 mg/day of fluvastatin with peginterferon/ribavirin in 94 naïve-to-treatment genotype 1b patients with high viral loads. The reported SVR rates in the fluvastatin and control arms were 63% and 42% ($P = 0.047$), respectively.

Combining all three studies (Georgescu *et al.*, Kondo *et al.* and ours, total sample size = 348), the reported SVR rates in the fluvastatin and control arms were 62% and 45% ($P = 0.0018$).

When our trial is viewed together with the two other RCTs using fluvastatin at 20 mg/day, the evidence is growing that fluvastatin improves the SVR rate when given to naïve-to-treatment genotype 1 HCV patients.

The mechanism of statin action against hepatitis C is poorly understood. Hypothetically, if the effect is related to changes in extracellular cholesterol, one has to account for the observation that fluvastatin is the weakest LDL-lowering statin and yet it has the strongest anti-HCV effect of all the statins tested [2]. Moreover, it is at the lowest approved dose for hypercholesterolaemia, 20 mg, for which fluvastatin has the greatest anti-HCV effect [3]. In retrospective analysis, some have tried to relate outcomes of peginterferon

alfa/ribavirin double therapy to the baseline serum LDL or baseline total cholesterol. In the largest *post hoc* analysis of statin and serum cholesterol (IDEAL trial), statin use was determined to be an independent factor from cholesterol as a predictor of response to peginterferon/ribavirin [12]. Later analysis of a smaller group from the IDEAL trial suggested that serum LDL cholesterol was strongly associated with the IL28B genotype and that it was this latter parameter that was more directly related to SVR outcome with peginterferon/ribavirin than cholesterol [13]. In our prospective work that delineated fluvastatin to have the strongest anti-HCV effect at 20 mg/day, we were unable to relate baseline LDL or changes in serum LDL to antiviral effect [3]. In the current work, there were no differences between groups in regard to baseline serum LDL or total cholesterol (Table 1).

The limitations of our study include a time period before which IL28B genotypes were appreciated or commercially available. As with many VA studies, ours tested only men. Liver biopsies were not performed; however, platelet counts are a practical surrogate, and these counts did not differ between groups. Based upon our retrospective study of statins[8], we planned an enrolment of 80 patients to reduce the possibility of type 2 error below the typically accepted level of 20%. With the prospective advent of protease inhibitors, it became increasingly difficult to enrol patients. Our closing study number was 45. Finally, the data reported for simvastatin are only preliminary in nature.

The relevance of the addition of fluvastatin to peginterferon/ribavirin in the era of HCV protease inhibitors may be greatest as cost-effective improvement in SVR for resource-limited areas. The current price for adding only the cost of the tablets for boceprevir or telaprevir ranges from US $28 000 to $55 000 per treated patient, respectively [14]. This does not include the cost of the peginterferon/ribavirin component or the expense of medical management. In contrast, the 20-mg capsule of fluvastatin was approved in generic form by the FDA on 13 April 2012. Prices for the generic version are not immediately available, but will likely become a US dollar per capsule as in other countries [15]. The 48-week cost of fluvastatin will then be US $336. There has not been a noninferiority head-to-head trial of fluvastatin triple therapy *vs* protease inhibitor triple therapy to compare SVR outcome.

Development of fluvastatin for HCV purposes has been slowed by the nonproprietary status of the drug and the persisting mythological paradigm of statin-induced hepatotoxicity [16–19]. It is relevant that the FDA recently revised all statin labels to state that monitoring of statins with liver tests is no longer recommended [19]. The 20-mg dose of fluvastatin has thus far been shown to be safe in HCV patients either alone or when added to peginterferon/ribavirin for 48 weeks.

The future of hepatitis C treatment seems to be heading towards combinations of oral antiviral agents. Given the positive results of the three randomized controlled trials reported here, further studies of fluvastatin for use against HCV as part of a multidrug regimen are needed.

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