Sofosbuvir Is the Major Contributor to Elevation of Blood Cholesterol and Low-density Lipoprotein During HCV Treatment With DAAs

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Abstract

Background and aims: Worsened lipid profiles were observed in chronic hepatitis C (CHC) patients during direct-acting antivirals (DAAs) treatment, among which combination drugs confounded the effect of individual ingredient on lipid. Tenofovir alafenamide (TAF) also worsened lipid profiles in HIV patients. Structural similarity between sofosbuvir (SOF) and TAF prompted us to investigate rapid increase in total cholesterol (TC) and low-density lipoprotein (LDL) in CHC patients treated with SOF-based DAAs.

Methods: A retrospective study was performed to analyze 487 CHC patients receiving DAAs with SVR12. Laboratory data were analyzed by logistic regression to determine relative risks of TC and LDL of SOF-based regimens over non-SOF-based regimens. Week 4 to baseline ratios of serum TC or LDL between regimens were compared by Mann-Whitney's test.

Results: 487 patients were treated with Harvoni® (SOF-based, 206 patients), Epclusa® (SOF-based, 124 patients), Maviret® (non-SOF-based, 122 patients), or Zepatier® (non-SOF-based, 35 patients). At week 4 during drug treatment, Harvoni®, Epclusa®, and Maviret® induced statistically significant elevation of TC and LDL, but Zepatier® did not. SOF-based regimens had 2.72-fold higher relative risk (RR) causing 10% elevation of TC (95% CI: 1.84-4.02, $p < 0.001$) and 2.04-fold higher RR causing 10% elevation of LDL (95% CI: 1.39-3.01, $p < 0.001$) than non-SOF-based DAAs.

Conclusion: SOF-based DAAs were associated with significantly larger amplitude of increases in TC and LDL than non-SOF-based regimens during the initial 4 weeks of treatment, but the amplitude was not sustained to SVR12.

Introduction

Hepatitis C virus (HCV) is one of the major causes of liver-related morbidity and mortality,(1) estimating infection of approximately 180 million people worldwide.(2) The HCV life cycle is initiated by binding of virus particles to hepatocellular receptors, endocytosis, fusion of HCV glycoproteins with endosomal membranes, acidification of endosome, and release of the viral genome into cytosol for replication(3). Internal ribosome entry site (IRES)-mediated translation of incoming viral RNA enables viral gene expression and processing, and replication occurs in the “membranous webs”(4). Following replication, genomic RNAs in complex with NS5A protein transit to lipid droplets, where core protein localizes and virion assembly occurs(5). After acquiring apolipoproteins B and E (apoB and apoE), components of VLDL (very low-density lipoproteins) and LDL, HCV infectious particles egress in a manner that parallels the VLDL secretory pathway(6, 7). HCV-infected patients have a prevalence of hepatic steatosis twofold higher than in HBV-infected patients,(8, 9) demonstrating a clear correlation between HCV infection and non-alcoholic fatty liver disease. These patients are also more likely to present decreased serum levels of apoB-bearing lipoproteins because HCV seizes these lipoproteins.(10, 11)

HCV nonstructural proteins 4B, 5A and 5B constitute a complex for RNA replication. The RNA translates into a polyprotein processed by viral NS3/4A and host proteases to generate structural proteins for viral assembly and nonstructural proteins involved in RNA replication.(12) Currently, direct-acting antivirals (DAAs), which have replaced interferon, are the standard treatment for HCV infection.(13, 14) According to mechanisms of action and therapeutic targets, DAAs are classified into four categories: nonstructural proteins 3/4A (NS3/4A) protease inhibitor, NS5A replication complex inhibitor, and NS5B nucleoside and non-nucleoside polymerase inhibitor.(15) In the class of NS5B nucleoside polymerase inhibitor, sofosbuvir (SOF) is the only drug and plays an important role in the combination of other DAAs for HCV treatment.(13, 14)

Although DAAs provide well-tolerated, safe, and highly efficacious outcomes,(16) several studies reported worsened lipid profiles in chronic hepatitis C (CHC) patients during DAAs treatment.(17, 18) SOF-based regimens appeared to have greater effect on LDL elevation. In the study by Meissner *et al.*, the patients treated with SOF/ribavirin had significantly increased levels of low-density lipoprotein (LDL) from baseline to the end of treatment and to post-treatment week 48.(17) Younossi *et al.* also found significantly increased LDL from baseline to the end of treatment and to post-treatment week 4 in CHC patients treated with SOF/ledipasvir.(18)

HCV virion is tightly associated with hepatocyte-derived lipoproteins to form a lipid-laden particle, called lipo-viro-particle. It was thought that HCV hijacks lipoproteins that are released to the blood after clearance of the virus by DAAs. Given that the concept is true, all DAA regimens would have equivalent effects on lipid profiles of the blood. In this report, we performed retrospective analysis based on structural similarity between TAF (tenofovir alafenamide) and SOF (Fig. 1A) and the observation that patients given TAF for HIV (human immunodeficiency virus) infection had elevated cholesterol level(19-21). Therefore, we hypothesized that SOF may be the major contributor to cholesterol and LDL elevations during DAAs treatment for patients infected by HCV. The mechanism may be related to the phosphoramidate side chain that is cleaved from sofosbuvir to produce an active nucleotide analogue, GS-461203 (2'-deoxy-2'- α -fluoro- β -C-methyluridine-5'-triphosphate).(22) (Fig. 1B)

Methods

Study population

The study retrospectively enrolled HCV-infected patients who received DAAs treatment for 8 or 12 weeks at Taipei Veterans General Hospital from September 2018 to August 2020. All patients were aged above 20, male or female and had chronic HCV infection, defined as detectable anti-HCV antibody and HCV RNA level in the serum for more than 6 months. Patients were excluded from the study if they had decompensated cirrhosis. The study was approved by the Institutional Review Board of Taipei Veterans General Hospital and was conducted in accordance with the principles of Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice. All patients read and signed informed consent before drug prescription and study-related procedure.

Study design

Baseline demographic data were collected before treatment. Hemogram, serum biochemical profiles (albumin, total bilirubin, direct bilirubin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], creatinine, international normalized ratio [INR], estimated glomerular filtration rate [eGFR]), anti-HCV, hepatitis B virus surface antigen (Abbott Architect HBsAg qualitative assay, Abbott Laboratories), HCV RNA and HCV genotype (Abbott RealTime HCV Genotype II, Abbott Laboratories, Abbott) were obtained from all patients. Hemogram and serum biochemistry were collected at weeks 1, 4, and SVR12. Non-cirrhotic patients were treated with *DAA*s as suggested in package insert, with or without with weight-based RBV (Robatrol®, 200 mg capsule, Genovate Biotechnology Co., Ltd. Taiwan; 1200 mg daily if the body weight $\geq$ 75 kg; 1000 mg daily if the body weight <75 kg) for 8 or 12 weeks. The DAA regimens included SOF/LED (sofosbuvir 400 mg/ledipasvir 90 mg, *Harvoni*®, 206 patients), SOF/VEL (sofosbuvir 400 mg/velpatasvir 100 mg, Epclusa®, 124 patients), GLE/PIB (glecaprevir 100 mg/pibrentasvir 40 mg, Maviret®, 122 patients), and ELB/GRA (elbasvir 50 mg/grazoprevir 100 mg, Zepatier®, 35 patients).

Virologic assessment

On-treatment effectiveness was assessed by detecting serum HCV RNA levels at weeks 4 and 12. The effectiveness at the end of treatment was SVR12, defined as serum HCV RNA level < LLOQ 12 weeks after completed treatment.

Statistical analyses.

All analyses were performed using STATA (12th ed., developed by StataCorp LLC, College Station, TX, USA). The pre-treatment patient characteristics were shown in median (range) and percentages as appropriate and compared by Mann-Whitney's test and χ^2 with Fisher's exact test. The effectiveness of treatment during and after drug administration was shown in number and percentages. Week 4 to baseline ratios of serum cholesterol or LDL between regimens were compared by Mann-Whitney's test or logistic regression. All statistics were two-tailed, and the results were considered statistically significant when a *p* value was < 0.05.

Results

Patient characteristics

Four hundred and eighty-seven CHC patients achieving SVR12 were included in the study (Table 1). The median age was 63 years, and 247 patients were male (50.7%). Four hundred and fifty-one patients were treatment-naïve (92.6%), and 35 had HBV co-infection (7.2%). No patient received antiviral therapy for HBV, and neither developed HBV reactivation nor hepatitis flares during DAA therapy. Forty-one patients had HIV co-infection, who took anti-HIV drugs. The median $\log_{10}$ HCV RNA level was 6.18. One hundred and ninety-six patients had a baseline viral load < 800,000 IU/mL (40.3%). One hundred and one patients had a Fib-4 fibrosis stage of F3 (20.8%), and 54 patients, F4 (11.1%) (Table 1).

Effectiveness

Four hundred and ninety-five patients were treated with different DAA regimens. Four hundred and eighty-seven patients achieved SVR12. The SVR12 rates for SOF/VEL, SOF/LED, GLE/PIB, and ELB/GRA were 100% (124/124), 99.5% (206/207), 94.6% (122/129), and 100% (35/35), respectively (Table 2).

Changes in cholesterol and low density lipoprotein at week 4

Three hundred and thirty patients were treated with SOF-based regimens (124 SOF/VEL and 206 SOF/LED), and 157 patients were treated with non-SOF-based (122 GLE/PIB and 35 ELB/GRA) with or without ribavirin for 8 or 12 weeks as shown in Table 1 (DAA regimens). At week 4, elevated total cholesterol (TC) (Fig. 2A) and low density lipoprotein (LDL) (Fig. 2B) were noted in patients treated with SOF/VEL ($p < 0.001$), SOF/LED ($p < 0.001$), and GLE/PIB (TC, $p = 0.002$; LDL, $p < 0.001$) but not in patients treated with ELB/GRA (TC, $p = 0.259$; LDL, $p = 0.144$). The elevations were sustained at SVR12 ($p < 0.001$). However, the ELB/GRA group showed higher TC and LDL at SVR12 than baseline (TC, $p = 0.035$; LDL, $p = 0.037$).

Amplitudes of changes in TC and LDL between SOF- and non-SOF-based regimens

Amplitudes of changes in serum TC and LDL from baseline to week 4 (or SVR12) were expressed as $\log_{10}[(\text{Week 4 or SVR12})/\text{Baseline}]$ and shown at Y axis of Fig. 3. SOF-based regimens caused significantly larger amplitude of change in TC (Fig. 3A, $p < 0.001$) and LDL (Fig. 3B, $p < 0.001$) at week 4 compared to non-SOF-based regimens. These changes were not sustained at SVR12 (TC, $p = 0.884$; LDL, $p = 0.475$). The stratified analyses compared different two regimens and showed that there was no significant difference in $\log_{10}[\text{Week4}/\text{Baseline}]$ change of both TC (Fig. 3C, $p = 0.361$) and LDL (Fig. 3D, $p = 0.248$) between the two SOF-based regimens, SOF/VEL and SOF/LED. The statistically significant changes in TC and LDL were noted at these two-regimen comparisons: SOF/VEL vs GLE/PIB (TC, $p = 0.001$; LDL, $p = 0.010$), SOF/LED vs GLE/PIB (TC, $p < 0.001$; LDL, $p < 0.001$), and SOF/LED vs ELB/GRA (TC, $p < 0.001$; LDL, $p = 0.011$). The p value of TC at SOF/VEL vs ELB/GRA was 0.017, and that of LDL was 0.070. These data suggested that SOF was associated with the major inductor of higher week-4 lipid change.

Incidence comparisons of increased TC or LDL in SOF- and non-SOF-based regimens.

To make TC and LDL elevations easy to understand, we classified week-4 TC and LDL changes to increases $> 10\%$ ($[\text{Week4}/\text{Baseline}] > 1.1$) and $> 25\%$ ($[\text{Week4}/\text{Baseline}] > 1.25$) by patient numbers (Table 3). The SOF-based regimens showed higher incidences of increases in TC and LDL $> 10\%$ (TC, $p < 0.001$; LDL, $p < 0.001$) or $> 25\%$ (TC, $p = 0.003$; LDL, $p = 0.001$) (Table 3). Relative risk (RR) of TC elevation $> 10\%$ for SOF-based regimens was 2.72-fold higher than non-SOF-based regimens (95% CI: 1.84-4.02, $p < 0.001$), and that of LDL was 2.04 (95% CI: 1.39-3.01, $p < 0.001$) (Table 4). RR of TC elevation $> 25\%$ for SOF-based regimens was 2.11-fold higher than non-SOF-based regimens (95% CI: 1.28-3.47, $p = 0.003$), and that of LDL was 2.04 (95% CI: 1.36-3.06, $p = 0.001$) (Table 4).

There were no significant differences in week-4 TC and LDL elevations between two SOF regimens (SOF/VEL and SOF/LED) and between two non-SOF regimens (GLE/PIB and ELB/GRA) in either increase > 10% or >25%. However, in TC > 10%, all SOF vs non-SOF (SOF/VEL vs GLE/PIB, SOF/VEL vs ELB/GRA, SOF/LED vs GLE/PIB, and SOF/LED vs ELB/GRA) showed significant differences in TC elevation. In LDL > 10%, SOF/LED caused significant higher risk in LDL elevation than GLE/PIB and ELB/GRA. In TC or LDL > 25%, SOF-based regimen still showed significant higher risk in some SOF vs non-SOF paired comparisons. These statistics gave further evidence for SOF in worsened week-4 lipid profiles. The SOF-based lipid-elevation effects were not seen at SVR12 (Supplementary Table 1).

Discussion

DAAs have been shown to worsen lipid profiles during CHC treatment. To the best of our knowledge, this study is the first retrospective analysis to evaluate the effect of SOF-based DAAs on changes in lipid profiles. Our results showed that compared with non-SOF DAAs, SOF-based DAAs were associated with more rapid increases in TC and LDL during the initial 4 weeks of treatment than the non-SOF counterparts. However, the SOF-potentiated effects were not sustained at the end of treatment. A further comparison of SOF/VEL or SOF/LED with GLE/PIB and ELB/GRA revealed a similar trend. It is interesting to note that ELB/GRA did not cause TC and LDL elevation at week 4. Very limited literature documented association of ELB/GRA with lipid worsening during CHC treatment. Sun *et al.* reported 24 cases, 13 treated with ELB/GRA and 11 with SOF/LED, showing significant elevation of cholesterol at week 4(23), which we think to be the effect of SOF/LED rather than ELB/GRA. However, at SVR12, TC and LDL tended to rise in ELB/GRA group compared with its baseline (TC, $p = 0.035$; LDL, $p = 0.037$, Fig. 2).

Combination DAAs have been the treatment standard for CHC. Our data provide strong evidence that SOF-based DAAs resulted in higher elevation of TC and LDL than non-SOF-based regimens at week 4 after drug administration. Since the two kinds of regimens achieved similar SVR12, viral clearance appeared not to be the sole mechanism to account for different TC and LDL changes between the two. We compared three compounds, sofosbuvir, tenofovir alafenamide (TAF), and tenofovir disoproxil fumarate (TDF) and found that SOF and TAF have similar phosphoramidate side chains (Fig. 1A). Milinkovic *et al.* reported changes in lipid profile in HIV patients treated with TDF or TAF. After switching from TDF to TAF, mean total cholesterol increased from 186 ± 37 mg/dl at baseline to 206 ± 43 mg/dL and 204 ± 43 mg/dL at weeks 12 and 24 ($p < 0.001$), and the increase in total cholesterol was mainly due to an increase in LDL-cholesterol.(20) Similar lipid changes were reported by other HIV investigators.(21, 24)

SOF and TAF are nucleotide prodrugs that are converted to active compounds by enzymatic cleavage of phosphoramidate side chain. SOF decomposed to GS-060965, phenolate ion, and propan-2-yl 2-aminopropanoate within hepatocytes (Fig. 1B).(25) Since TDF does not cause change in lipid as do SOF and TAF, the cleaved products from phosphoramidate may be the agents that promote b-lipoprotein synthesis and secretion by hepatocytes.

For CHC patients, SOF-based DAAs rapidly and significantly elevated TC and LDL levels during the initial 4 weeks of treatment, but the higher amplitudes of changes in TC and LDL tended to disappear at the end of treatment. It could be deduced from the chemical structures of SOF and TAF that the cleaved products phenolate ion and propan-2-yl 2-aminopropanoate from the phosphoramidate side chain may promote b-lipoprotein synthesis and secretion initially and then induce more enzymes to destroy them with time, so TC and LDL levels jump transiently and then decline.

Our results showed trends of increases in TC and LDL at week 4 and SVR12. Some reports showed the increases in TC or LDL disappeared after treatment.(26, 27) Other studies suggested the elevated LDL continued to post-treatment one year.(28-31) The main reason for the inconsistency was that most of these studies were single-arm studies without placebo controls. Additionally, both Younossi *et al.* and Pedersen *et al.* observed that genotype 3 patients had significantly increased LDL during DAAs treatment, but genotype 1 or genotype 2 patients did not.(32, 33) As the majority of the included patients in the present study were genotype 1 (59.6%) and genotype 2 (32.9%) patients (Table 1), changes in LDL would be less, consequently reducing the difference between treatment groups. Furthermore, genetic factors have been reported in association with changes in LDL. In the study by Emmanuel *et al.*, the *IFNL4-ΔG* carriers had significant increases in LDL during DAAs treatment and at post-treatment one year, but the patients with *IFNL4-TT/TT* did not.(34) In the study by Morihana *et al.*, the difference in LDL between sofosbuvir/ledipasvir and daclatasvir/asunaprevir disappeared after the end of treatment. However, the *IL28B TG/GG* patients continued to have increased LDL from the end of treatment to post-treatment two years, whereas the *IL28B TT* patients did not.(26) Because the current analysis did not consider these genetic factors, our results might be potentially confounded by these predictors.

Although it was common to observe increases in TC and LDL during DAAs treatment, a few studies analyzing risk factors for increased LDL during DAAs treatment revealed discordant findings. In the study by Morihana *et al.*, multivariate regression analysis showed that changes in LDL were negatively correlated with baseline LDL and HDL.(26) Hashimoto *et al.* reported that the decline of HCV core antigen from day 0 to day 1 was independently associated with amplitudes of changes in LDL but not with baseline LDL during DAA treatment.(35) The discordance highlighted the need of prospective large-scale long-term studies to elucidate the effect of DAAs on lipid profiles.

There were several limitations in this study. Firstly, lipid profiles are incomplete without HDL and triglyceride. Secondly, case numbers are uneven among DAA regimens. The third is that the included patients in this study were mainly those who achieved SVR12. In addition, we did not have lipid data of post-treatment long-term follow-up. Therefore, it deserves more comparative studies, which evaluate complete lipid profiles at different time points among DAAs regimens.

Declarations

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1. **Data Availability:** The datasets generated during and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.
2. **Animal Research:** no animal study in the manuscript
3. **Consent to Participate:** The study was approved by the Institutional Review Board of Taipei Veterans General Hospital and was conducted in accordance with the principles of Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice. All patients read and signed informed consent before drug prescription and study-related procedure.
4. **Consent to Publish:** All authors agree that the copyright is transferred to the journal in case of acceptance of the manuscript.
5. **Data Reproducibility:** data shown in tables and figures are repeated at least three times, and all are reproducible.
6. **Clinical Trials Registration:** This is not a clinical trial study
7. **Author Contribution:** All authors have contributed substantially to preparation of this manuscript including conception and design, execution, analysis, and interpretation of data, and drafting the article.
8. **Conflict of Interest:** All authors listed declare no conflict of interest.
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Tables

Due to technical limitations, table 1-4 is only available as a download in the Supplemental Files section.

Figures

A

Tenofovir alafenamide

Sofosbuvir

Tenofovir disoproxil fumarate

B

Figure 1

Structures of tenofovir alafenamide (TAF), sofosbuvir (SOF), and tenofovir disoproxil fumarate (panel A). TAF and SOF have similar phosphoramidate side chain (green and orange in the figure) that is cleaved from sofosbuvir to produce an active nucleotide analogue, GS-461203 (2'-deoxy-2'- α -fluoro- β -C-methyluridine-5'-triphosphate) (panel B).

Figure 2

Boxplots showing total cholesterol (TC) (panel A) and LDL (panel B) levels at baseline, week-4 and SVR12 during different DAAs treatment. Patient number: SOF/VEL (n=124), SOF/LED (n=206), GLE/PIB (n=122) and ELB/GRA (n=35). TC and LDL levels at baseline, week-4 and SVR12 were compared by paired sample t test.

Figure 3

Boxplots showing TC and LDL ratios of week 4/baseline and SVR12/baseline in SOF-based and non-SOF-based DAA (TC in panel A; LDL in panel B) and in different DAA regimens (TC in panel C; LDL in panel D). The Y-axis scale is the value of $\log_{10}[(\text{Week 4 or SVR12})/(\text{Baseline})]$. The differences were compared by Mann-Whitney's test.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementarydata.pptx](#)
- [TablesSR.ppt](#)