Effect of Sofosbuvir Plus Daclatasvir in Hepatitis C Virus Genotype-4 Patients: Promising Effect on Liver Fibrosis

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Background/purpose: The effect of sofosbuvir and daclatasvir in treatment of genotype 4 Hepatitis C Virus (HCV) is not well documented. This study investigated the safety and efficacy of sofosbuvir plus daclatasvir with or without ribavirin in treatment of HCV genotype 4 patients. The impact of therapy on liver fibrosis as well as the role of IL18 polymorphism in therapeutic outcome was assessed. **Methods:** One hundred HCV genotype 4 patients were categorized into 2 groups. The group 1 comprised treatment naïve patients, with total serum bilirubin ≤ 1.2 mg/10⁻¹ L, serum albumin ≥ 3.5 g/10⁻¹ L, INR ≤ 1.2 , and platelet count $\geq 150 \times 10^9$ /L. This group was treated with sofosbuvir plus daclatasvir for 12 weeks. The group 2 included Peg-IFN- α -or sofosbuvir treatment experienced, or patients with at least 2 of the following findings: total serum bilirubin > 1.2 mg/10⁻¹ L, serum albumin < 3.5 g/10⁻¹ L, INR > 1.2 , and platelet count $< 150 \times 10^9$ L⁻¹. Group 2 was treated with sofosbuvir–daclatasvir + ribavirin for 12 weeks, with the exception of sofosbuvir treatment experienced patients, who were treated with sofosbuvir/daclatasvir + ribavirin for 24 weeks. **Results:** Sustained Virological Response (SVR12) (undetectable viremia 12 weeks post-treatment), was 93.3% in group 1 and 87.5% in group 2 (total = 91%). Such high efficacy was accompanied with tolerable adverse effects as well as with significant improvement in liver fibrosis. No significant association was observed between IL18 polymorphism (rs1946518) at position –607 and achievement of SVR12 in HCV patients after treatment. **Conclusion:** Sofosbuvir plus daclatasvir, with or without ribavirin achieved high efficacy and safety in HCV genotype 4 patients. Their effects were accompanied with attenuation of liver fibrosis. Further wider-scale studies are needed to evaluate the actual role of IL18 polymorphisms in treatment response with sofosbuvir/daclatasvir. (J CLIN EXP HEPATOL 2018;8:15–22)

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Globally, Hepatitis C Virus (HCV) is a leading cause of liver cirrhosis and hepatocellular carcinoma. It affects 180 million people worldwide; about 3% of the world population.¹ Egypt has the highest prevalence of HCV. The number of annual new infection is about

150 000. Genotype 4 is the predominant genotype in Egypt; as it represents 90% of infected Egyptians.^{2,3}

In 2011, the emergence of new medications, named Directly Acting Antivirals (DAA), represented a major advance in treatment of HCV.⁴ These drugs targeted the viral proteins implicated in viral replication. Among DAA drugs, sofosbuvir and daclatasvir showed promising efficacy.

Sofosbuvir is a nucleotide analog HCV NS5B polymerase inhibitor and daclatasvir is HCV NS5A replication complex inhibitor. Both drugs achieved high efficacy and safety in genotype 1, 2, and 3 and were administered orally once daily in a dose of 60 mg and 400 mg, respectively.^{5–10} However, their effects in genotype 4 were not well documented.

Pharmacogenomics of DAA could participate in optimizing treatment decision taking and identify predictors of response.¹¹ Several studies suggested a possible role of IL28 or Single Nucleotide Polymorphisms (SNPs) of the gene IL-18 at positions –607 in clearance of HCV infection.^{11,12} There were no data, so far, concerning the role of IL18 polymorphism in HCV-genotype 4 patients regarding therapeutic outcome of sofosbuvir and daclatasvir therapy.

The current study was designed to investigate the efficacy and safety of sofosbuvir/daclatasvir, with or

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Abbreviations: DAA: Direct Acting Anti-viral; FIB 4: Fibrosis Score 4; HCV: Hepatitis C Virus; IL-18: Interleukin 18; INF: Interferon; NS: Non-Structural; PCR: Polymerase Chain Reaction; RFLP: Restriction Fragment Length Polymorphism; RNA: Ribonucleic Acid; SNPs: Single-Nucleotide Polymorphisms; SVR12: Sustained Virologic Response 12 Week Post Treatment

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without ribavirin in treatment of HCV genotype 4, as well as their effect on the liver fibrosis. Additionally, the study tried to assess the relationship between IL18 polymorphism (rs1946518) at position -607 C/A and response to sofosbuvir/daclatasvir with or without ribavirin therapy.

METHODS

Patients

A total of 100 patients having chronic HCV genotype 4 infection, who were scheduled to receive combined sofosbuvir/daclatasvir with or without ribavirin, were chosen from Liver Unit of Minia University Hospital. All patients volunteered to participate in the study and were prospectively followed up for the full duration of the study, which was 9 months, during which the patients were evaluated every 4 weeks. Patients were subjected to thorough history taking, clinical examination, and laboratory investigations including serum transaminases, bilirubin, albumin, complete blood count and alpha feto-protein as well as abdominal ultrasound. Eligible patients had chronic infection with genotype 4 HCV, aged between 21 and 75 years, with plasma HCV RNA $\geq 10^4$.

Exclusion criteria included co-infection with hepatitis B or human immune-deficiency viruses, coexistent autoimmune liver diseases, or other coexistent chronic liver diseases as decompensated liver disease or hepatocellular carcinoma, as well as pregnancy, renal impairment, or having creatinine clearance < 60 mL/min; hemoglobin < 11 g/dL; platelets $< 50 \times 10^9$ /L; total bilirubin > 3 mg/dL or albumin < 3 g/dL.

Study Design

This work was conducted according to the ethical rules of the Faculty of Medicine, Minia University, Egypt, and approved by the faculty board. The study conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent was obtained from all patients. Patients were categorized into 2 groups, where the group 1 was characterized by being treatment-naïve patients, with total serum bilirubin ≤ 1.2 mg/ 10^{-1} L, serum albumin ≥ 3.5 g/ 10^{-1} L, International Normalization Ratio (INR) ≤ 1.2 and platelet count $\geq 150 \times 10^9$ /L. This group was treated with sofosbuvir/daclatasvir for 12 weeks. The group 2 included Peg-IFN- α -or sofosbuvir treatment-experienced patients, or patient having at least 2 of the following characteristics: total serum bilirubin > 1.2 mg/ 10^{-1} L, serum albumin < 3.5 g/ 10^{-1} L, INR > 1.2 , or platelet count $< 150 \times 10^9$ /L. This group was treated with sofosbuvir/daclatasvir + ribavirin for 12 weeks except sofosbuvir treatment experienced patients, who were treated with sofosbuvir/daclatasvir + ribavirin for 24 weeks. The effect of therapies on liver fibrosis was assessed by Fibrosis Score

4 (FIB-4), a noninvasive technique, employing 4 parameters according the following equation:

$$\text{Age (year)} \times \text{AST (IU/L)} / (\text{platelet count (} 10^9/\text{L)} \times \sqrt{\text{ALT (IU/L)}}$$

where FIB-4 score < 1.45 = F0–F1 (mild fibrosis) and FIB-4 score > 3.25 = F3–F4 (severe fibrosis or cirrhosis).^{13,14}

Both sofosbuvir and daclatasvir were administered, orally once daily, in a dose of 400 mg and 60 mg, respectively. The dose of ribavirin was 600–1000 mg in divided doses according to patient tolerability. The treatment regimen was in consistence with the protocol of Egyptian National Committee for Controlling HCV (NCCVH) and the guidelines of European Association for the Study of the Liver (EASL recommendation on treatment of HCV 2016).¹⁵

Assessment of Virological Response

Virological response was assessed by HCV-RNA PCR using the Roche Ampliprep/COBAS TaqMan HCV Test (v2.0; Roche Molecular Systems, Inc., Branchburg, NJ), which has an LLOQ of 12 IU/mL. HCV-RNA PCR was done at 4 weeks as well as at 12 weeks after the end of treatment. If HCV-RNA was undetectable 12 weeks after the end of treatment, the patient was considered to have SVR12. Virologic relapse was defined as the presence of serum HCV RNA ≥ 12 IU/mL at any time during the post-treatment follow-up period. Treatment failure was defined as inability of the patient to complete the treatment regimen due to intolerance of adverse effects.

Assessment of Drugs Safety

Safety data were collected monthly during treatment and 4 weeks after stoppage of treatment. Collected data reported the adverse events and clinical laboratory tests, as liver function tests, serum creatinine, and complete blood count. Concomitant medication intake was also recorded.

Assessment of Liver Fibrosis

Liver fibrosis was assessed in all studied patients using FIB-4 test before starting the treatment and at 12 weeks after the end of therapy.

Detection of IL-18 Polymorphism (–607 C/A)

Nighty six HCV genotype 4 patients were included for detection of IL 18 (–607 C/A) polymorphism, where 5 mL blood samples were collected from all subjects in sterile tubes. Genomic DNA was extracted from whole blood using the established protocol as described.¹⁶ Genotyping of SNP –607 C/A (rs1946518) was carried out by PCR and RFLP assay. For rs1946518, oligonucleotide primers were used: (forward) 5'TTCTGTTGCAGAAAGTGTAAAAATTTT-3' and (reverse) 5'AAAGGATAGTTGATACAGGCCATT-3'. PCR conditions were: initial denaturation at 95 °C for 10 min, followed by 35 cycles of

denaturation at 94 °C for 30 s, annealing at 58 °C for 30 s, extension at 72 °C for 45 s, and final extension at 72 °C for 7 min. PCR products for rs1946518 were of 154 bp for the C allele and 125 and 28 bp for the A allele.¹⁷ To perform RFLP assay for rs1946518 genotype, amplicons were digested with fast digest DraI restriction endonuclease (Thermo scientific com). Dra I digestion of C allele yields fragments of 154 bp, whereas DNA containing allele A polymorphism yields fragments of 125 and 28 bp. Restriction digestion products for each were separated on agarose gel 3% for visualization on a UV trans illuminator.

End Points and Statistical Analysis

HCV-RNA PCR was done at 4 weeks as well as at 12 weeks after the end of treatment. If HCV-RNA was undetectable 12 weeks after the end of treatment, the patient was considered to have SVR12. Virologic relapse was defined as the presence of serum HCV RNA ≥ 12 IU/mL at any time during the post-treatment follow-up period. Treatment failure was defined as inability of the patient to complete the treatment regimen due to intolerance of adverse effects. The primary endpoint was undetectable viremia at 12 weeks after treatment (SVR12). The secondary endpoint was either undetectable viremia at 4 weeks (SVR4) weeks after treatment, virological relapse, or treatment failure.

The collected data were revised, organized, tabulated and statistically analyzed using Statistical Package for Social Sciences (SPSS) version 20.0 for windows. For efficacy analysis, all patients who started the protocol were included. Data are presented as the mean $\pm$ Standard Deviation (SD), mean $\pm$ Standard Error of Mean (SEM), frequency, and percentage. Chi-square (χ^2) and Fisher's exact tests were used for

comparison of categorical data. Descriptive analysis was performed to compare genotype frequencies using the Chi-square test for qualitative data and mean $\pm$ SD for quantitative data. Odd Ratios (OR) was calculated where and when applicable. Genotypic and allelic frequencies were assessed using Hardy-Weinberg equilibrium. Results were considered statistically significant when the *P*-value was less than 0.05.

RESULTS

Baseline Characteristic of the Patients

This study included 100 patients, where 60 patients were allocated in the group 1 and 40 in the group 2. The mean age was 48 ± 11 in group 1 and 52 ± 11 in group 2. Concerning the gender, 64 were males and 36 were females. From the total number of patients, 19 had diabetes mellitus, 17 had previously received interferon-alpha based therapy, 4 had previously received sofosbuvir + ribavirin therapy, 17 had severe fibrosis (FIB-4 > 3.25), 49 had moderate fibrosis, and 34 had mild fibrosis (FIB-4 score < 1.45) before the initiation of therapy (Table 1).

Effect of Sofosbuvir/Daclatasvir $\pm$ Ribavirin on Virological Response

In the group 1, 56 patients (93.3%) achieved SVR12 while 35 (87.5%) achieved SVR12 in the group 2 (Table 2). For both protocols, 91 patients (91%) achieved SVR12 while 5 patients relapse within 4 week post treatment. Four patients did not complete the study; 2 patients from each of the first and group 2s, but were included in the

Table 1 Demographic Data and Baseline Characteristics.

Parameter	Group 1 (n = 60) (SOF + DAC)	Group 2 (n = 40) (SOF + DAC + RIB)
Age (years)	46.5 $\pm$ 1.4	42.8 $\pm$ 1.8
Range	(21–74)	(23–75)
Gender	Male 45 (75%) Female 15 (25%)	Male 19 (47.5%) Female 21 (52.5%)
Albumin (g/10 ⁻¹ L)	4.1 $\pm$ 0.03	3.2 $\pm$ 0.01
Bilirubin (mg/10 ⁻¹ L)	0.68 $\pm$ 0.02	1.6 $\pm$ 0.1
HCV RNA (1 $\times$ 10 ⁴ IU/mL)	549.1 $\pm$ 53.8	656.7 $\pm$ 92.9
Platelet count (1 $\times$ 10 ⁹ /L)	225.5 $\pm$ 8.1	143.6 $\pm$ 4.0
INR	1.1 $\pm$ 0.2	1.3 $\pm$ 0.01
Treatment-experienced patients		
Peg-IFN- α	0 (0%)	17 (17%)
SOF-RIB	0 (0%)	4 (4%)
Fibrosis score		
Severe fibrosis	0 (0%)	17 (42.5%)
Moderate fibrosis	35 (58.3%)	14 (35%)
Mild fibrosis	25 (41.7%)	9 (22.5%)

Total n = 100, SOF: Sofosbuvir, DAC: Daclatasvir, RIB: Ribavirin, IFN- α : Interferon- α .

Table 2 Virological Response Among Studied Population, Total $n = 100$.

Studied group	Regimen of treatment	Total No.	SVR 12	Relapsers plus patients stopped treatment
Group 1	SOF/DAC	60	56 (93.3%)	4 (6.7%)
Group 2	SOF/DAC + RIB	40	35 (87.5%)	5 (12.5%)

SOF: Sofosbuvir, DAC: Daclatasvir, RIB: Ribavirin, INF- α : Interferon- α .

Table 3 Effect of SOF/DAC With or Without Ribavirin on Fibrosis Score, Total $n = 96$.

Treatment protocol	Fibrosis score	Pre treatment fibrosis	Post treatment fibrosis	P-value *
SOF/DAC without ribavirin	Mild fibrosis	24 (41.4%)	38 (65.5%)	<0.05 **
	Moderate fibrosis	34 (58.6%)	20 (34.5%)	
SOF/DAC with ribavirin	Mild	9 (23.7%)	22 (57.9%)	<0.05 **
	Moderate	14 (36.8%)	9 (23.7%)	
	Severe	15 (39.5%)	7 (18.4%)	

*Chi-square test was used.

**S: statistically significant difference ($P \leq 0.05$).

SOF: sofosbuvir, DAC: daclatasvir, RIB: ribavirin.

NB: four cases with mild, moderate and severe fibrosis stopped treatment due to complications.

statistics, two of them had severe fibrosis and developed hepatic de-compensation one month after initiation of therapy, one was a female patient with moderate fibrosis who stopped the treatment for unknown cause and withdrawn from the protocol, and the fourth case was a female patient with mild fibrosis and rheumatoid arthritis who developed severe arthralgia 15 days after starting therapy.

There were 5 relapsers, 2 in the group 1 and 3 in the group 2. Four of the relapsers were males and one was female. Three of the relapsers had moderate fibrosis, 2 had severe fibrosis and one patient was diabetic with previous

failure of both INF-based and sofosbuvir-ribavirin therapy. Among 21 treatment-experienced patients, only one patient was a relapser.

Effect of Sofosbuvir/Daclatasvir $\pm$ Ribavirin on Liver Fibrosis

In sofosbuvir/daclatasvir regimen (group 1), the patients with moderate fibrosis were decreased from 34 (58.6%) before treatment to 20 (34.5%); with subsequent increase of mild fibrosis from 24 (41.4%) to 38 (65.5%) after treatment (Table 3). In sofosbuvir/daclatasvir + ribavirin regimen (group 2), the patients with severe fibrosis were

Table 4 Side Effects and Laboratory Findings Among Studied Groups.

Parameters	Group 1 (SOF + DAC)	Group 2 (SOF + DAC + RIB)
Patients with any adverse effect	42 (72.4%)	32 (84.2%)
Patients with a serious adverse effect	0 (0%)	2 (5.26%)
Patients with adverse leading to discontinuation	0 (0%)	2 (5.26%)
Death	0 (0.0%)	0 (0.0%)
Adverse effect in more than 2% of patients		
Fatigue	39 (67.2%)	28 (73.7%)
Headache	24 (41.4%)	25 (65.8%)
Dizziness	16 (27.6%)	25 (65.8%)
Anorexia	15 (25.9%)	22 (57.9%)
Fever	4 (6.8%)	5 (13.2%)
Insomnia	2 (3.4%)	7 (18.4%)
Increased serum bilirubin	8 (13.8%)	29 (76.3%)
Decreased hemoglobin (<10 g/dL)	2 (3.4%)	7 (18.4%)
Increased platelet count	46 (79.3%)	28 (73.7%)

Total $n = 96$, SOF: Sofosbuvir, DAC: Daclatasvir, RIB: Ribavirin.

Figure 1 Distribution of IL-18 polymorphism gene. A: reveals the percentage of gene allele distribution in HCV patients. B: the percentage of C/C in responders (32 patients) compared to relapsers groups (0 patients) (35.2% versus 0%, respectively), and the percentage of A/C in relapsers (5 patients) compared to responders (59 patients) (100% versus 64.8% respectively), with no statistical significant between these groups, $P = 0.16$. C: PCR digestion for –607 polymorphism IL-18 gene allele: Agarose gel electrophoresis analysis of rs1946518 polymorphism in IL-18 gene. CC genotype produced only in 154 bp band and AC genotype produced 3 bands 154, 125 and 28 bp, respectively. M line represents the 50 bp molecular gene ruler DNA ladder used as a marker and 250 bp as a reference band (28 bp band not appear).

decreased from 15 (39.5%) before treatment to 7 (18.4%) after treatment. The patients with moderate fibrosis were decreased from 14 (36.8%) before treatment to 9 (23.7%) after treatment; with subsequent increase of mild fibrosis from 9 (23.7%) to 22 (57.9%).

Safety of Sofosbuvir/Daclatasvir $\pm$ Ribavirin

In group 1 and group 2, the reported adverse events were fatigue (67% and 74%), headache (41% and 66%), dizziness (28% and 66%), anorexia (26% and 58%), fever (7% and 13%), insomnia (3% and 13%), hyperbilirubinemia (14% and 76%), and anemia (2% and 7%), respectively (Table 4). In group 1, two patients could not complete the protocol. One of them was known rheumatoid arthritis who suffered acute arthralgia. The second patient withdrew from the study due to unknown cause. In group 2, two patients developed hepatic decompensation manifested by ascites

and increased serum bilirubin > 5 mg/dL. In both groups, platelet count was significantly increased (Table 4).

Frequency of IL18 Polymorphism (rs1946518) at Position –607

Figure 1A shows the main results of the distribution of IL18 polymorphism (rs1946518) at position –607 in chronic HCV genotype 4, where the frequency of genotypes CC was (33.3%) and of genotype AC was (66.7%). There was no statistical significant difference in distribution of IL18 polymorphism allele and HCV.

Figure 1B shows that Genotype C/C genotype was only present in responder (35.2%) while A/C genotype was present in responder cases (64.8%) as well as in relapsers (100%). There was no significant association between IL18 polymorphism (rs1946518) at position –607 and SVR12.

DISCUSSION

This study was dedicated to investigate the efficacy and safety of HCV genotype 4 using sofosbuvir/daclatasvir $\pm$ ribavirin. The results of this study suggest that sofosbuvir/daclatasvir with or without ribavirin were successful in treating HCV genotype 4 patients. Ninety one percent of the patients reached the primary endpoint of SVR12 in either naïve or treatment-experienced patients. Previous studies have evaluated the efficacy of all-oral DAA regimens in patients with HCV genotype 4.¹⁸ Most of these studies used small number of patients. The first studies of DAA plus interferon- α and ribavirin in HCV genotype 4 patients proved a high efficacy associated with side effects of interferon-alpha and ribavirin. Some studies showed that co-administration of daclatasvir with interferon-alpha plus ribavirin for 24 weeks, resulted in SVR12 rates of 82% (67 of 82) to 100% (12 of 12) in treatment-naïve patients with HCV genotype 4.^{9,19} In other HCV genotypes, two clinical trials had evaluated the effect of sofosbuvir in combination with daclatasvir; one was for treatment-naïve patients with HCV genotypes 1, 2 and 3 which reported that SVR12 was 100% of patients had genotype 1 and 86–100% in patients with the genotype 2 and 3.¹⁰ The second evaluated the combination of daclatasvir and sofosbuvir in 41 HCV genotype 1 patients who had previously failed protease-inhibitor-based triple therapy with either telaprevir or boceprevir and were treated with 24 weeks of sofosbuvir/daclatasvir $\pm$ ribavirin. Impressively, SVR12 rates were 95–100% with combination of ribavirin or not, demonstrating that this combination of sofosbuvir with daclatasvir is an effective therapy even in people with NS3A protease inhibitor resistance.²⁰ Recently, Poordad et al.²¹ had reported that the pan-genotypic efficacy and safety of sofosbuvir/daclatasvir with ribavirin even in patients with post-liver transplantation recurrence or advanced cirrhosis.

The results of our study showed that only 9 patients (out of 100) did not reach SVR12. Only 5 patients among those who completed the study had relapsed within 4 weeks after the end of treatment. Out of the 5 relapsers, 3 patients were on sofosbuvir/daclatasvir with ribavirin and 2 patients were on sofosbuvir/daclatasvir without ribavirin. Three patients had moderate fibrosis and 2 had severe fibrosis. The cause of relapse was not clear. In trial to search for the cause of relapse, the current study tested several possibilities including degree of liver fibrosis and IL-18 gene polymorphism. Interestingly, 7 out of 9 patients who could not reach the primary end point were considered having moderate to severe fibrosis. Such observation indicated the association between therapeutic failure and stage of fibrosis. In line with the current results, cirrhotic patients with HCV infection were reported to experience low response rate with interferon-based therapy or protease-inhibitor containing regimen in many studies.²² The exact relation between

cirrhosis and therapeutic outcome has not been identified yet. Interestingly, our results showed significant improvement in fibrosis score in either group. In support of the current results, recent study reported early improvement in liver fibrosis in sofosbuvir-based therapy, using noninvasive methods (fibroscan and Enhanced Liver Fibrosis score (ELF)) for assessment of fibrosis.⁷ Histopathological confirmation is needed to confirm such results. In line with the current results, a recent systematic review assessed the effectiveness of INF-free regimens, including sofosbuvir/daclatasvir in Child C cirrhotic patients, where they concluded that there is a significant improvement in liver function as indicated by improvement of Model for End-stage Liver Disease score (MELD score).²³

The results of the current study showed the safety profiles of sofosbuvir/daclatasvir with or without ribavirin therapy. In patients who completed the study, there were no clinically significant treatment-emergent adverse events in patients receiving sofosbuvir/daclatasvir without ribavirin. The low incidence of adverse events might attribute, at least in part, to short duration of treatment as compared to IFN-based therapy. In patients receiving sofosbuvir/daclatasvir + ribavirin, increased serum bilirubin and decreased hemoglobin were related to ribavirin drug. These findings previously reported by Wu et al.²⁴ suggested that ribavirin is a triggering factor of hemolytic anemia. On the other hand, the current study reported that 2 patients from group 2 developed hepatic decompensation one month after initiating therapy. Such findings were supported by Dyson et al.²⁵ who suggested a possible hepatotoxic effect caused by an unknown interaction or reaction to the drug combination; though the association with the DAA was not proven. These results indicated that close monitoring is essential while on DAA therapy; especially in patients with advanced liver disease. Given the timing of events, it is probable that the liver injury was drug-related. At the molecular level, the predominant circulating metabolite of sofosbuvir, GS-331007, is formed by dephosphorylation of nucleotide metabolites, accounts for approximately 78% of total systemic exposure and is principally excreted in urine. In advanced liver disease, the metabolism of Sofosbuvir may be altered leading to toxic liver injury.⁸ Further studies are needed to establish the underlying mechanism of possible sofosbuvir-induced hepatotoxicity, especially in advanced liver disease.

Daclatasvir is eliminated by hepatic metabolism and direct biliary excretion with 88% being excreted in feces. Biliary excretion of these drugs could be impaired in the setting of advanced liver disease or secondary to a bile transporter defect. This potential mechanism needs further evaluation.²⁶

Another patient, a known rheumatoid arthritis patient under small doses of prednisone and hydroxyquine, developed acute arthralgia and stopped therapy one month after starting the protocol. There was no solid explanation

of such case. Interaction during coadministration of sofosbuvir and/or daclatasvir with prednisone and/or hydroxyquinone has not been studied. However, the referenced Liverpool university website for hepatic drug interaction (www.hep_druginteractions.org) reported that drug interaction is unlikely.²⁷ Additionally, a recent study reviewed drug interaction with new hepatitis C drugs including daclatasvir and sofosbuvir, and concluded that drugs interaction of these drugs are generally moderate.²⁸

Interleukin-18 plays a significant role in the immune response by enhancing T cell response, regulating interferon- γ production and promoting the development of Th1 immune responses. It has been reported that genetic host factors might attribute to the therapeutic outcome and clearance of HCV infection.²⁹ Therefore, the current study evaluated the association between IL-18 gene polymorphism and therapeutic response to sofosbuvir/daclatasvir therapy.

The present study showed that distribution of genotypes CC or AC of IL-18 polymorphism at position -607 between patients was not significantly different; indicating that C/C or AC allele are not predictors for HCV chronicity. In consistence of the current findings, the result of Yang and Liu³⁰ and the result of Abdelraheem³¹ indicated that there were no evidence for association between -607 C/A polymorphism and chronicity HCV infection. On the other hand, studies by An et al.¹⁷ and Santos et al.¹² reported that patients carrying genotype A/C at position -607 were found to be at higher risk of persistent HCV infection. Further studies are needed to explore this point.

There was a higher proportion of AC genotype in responders compared to relapsers. However due to very small numbers in the non-responder group this difference did not reach statistical significance. Accordingly; the study did not have enough power to evaluate role of IL18 polymorphism in treatment response. To best of knowledge, this study was the first that reported the impact of IL-18 promoter variants in chronic HCV patients treated with sofosbuvir/daclatasvir with or without ribavirin in genotype 4 HCV patients. Further large scale study is needed to investigate this point.

CONCLUSION

Sofosbuvir plus daclatasvir, with or without ribavirin, achieved high efficacy (more than 90%) and well tolerated in genotype 4 HCV patients. They were equally effective either in naïve or treatment-experienced patients. Efficacy and safety of sofosbuvir/daclatasvir, with or without ribavirin, were accompanied with attenuation of liver fibrosis score as assessed by FIB-4. The proportion of AC genotype was higher in responders compared to non-responders; however, due to very small numbers in the non-responder group this did not reach statistical significance.

LIMITATION OF THE STUDY

The effect of tested drugs on liver fibrosis was limited because liver biopsy is the standard test for accurate assessment of liver fibrosis. Further studies are essential to confirm such results.

CONFLICTS OF INTEREST

The authors have none to declare.

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