Influence of different regimens of direct acting antiviral agents (DAAS) with or without ribavirin used for chronic hepatitis C treatment on the cardiac muscles in Egypt

Ahmed Hosny El-Adawy1*, Ahmed Youssef Altonbary2, Hazem Hakim2, Doaa Helmy Bakr3, Engy Foda3
1 Department of cardiovascular medicine, faculty of medicine, Mansoura University, Mansoura 35516, Egypt
2 Department of gastroenterology and hepatology, faculty of medicine, Mansoura University, Mansoura 35516, Egypt
3 Department of clinical pathology, faculty of medicine, Mansoura University, Mansoura 35516, Egypt

Abstract

Background: Infection with Hepatitis C virus (HCV) is of significant public-health encumbrance in Egyptian population that afford the considerable predominance rate worldwide. This study was aimed to evaluate the correlation between the different treatment regimens on cardiac cardiovascular complication. Methods and Results: In this study, 390 patients diagnosed as HCV infection in Mansoura, Egypt were sectioned into four groups. Group A treated with ledipasvir and sofosbuvir (LED + SOF), group B received simprevir and sofosbuvir (SIM+SOF), group C treated sofosbuvir and daclatasvir (SoF+DCV) and group D received with triple combination therapy of sofosbuvir, daclatasvir and ribavirin (SOF+DCV+ RBV). The full hepatological assessment, blood analysis and clinical investigation were performed. All participants went through a cardiac assessment for detection of development of cardiovascular changes. There was significant elevation in levels of AST, ALT, serum albumin, platelet count, hemoglobin concentration and the Child classification between the studied groups. There was significant difference in the CMR results during the study especially in fourth group (SOF+DCV+RBV) group. The full hepatological assessment, blood analysis and clinical investigation were performed. All participants went through a cardiac assessment for detection of development of cardiovascular changes. There was significant elevation in levels of AST, ALT, serum albumin, platelet count, hemoglobin concentration and the Child classification between the studied groups. There was significant difference in the CMR results during the study especially in fourth group (SOF+DCV+RBV) group. No statistical difference regarding pericardial effusion. There was significant difference in the CMR results during the study especially in fourth group (SOF+DCV+RBV) group. No statistical difference regarding pericardial effusion. There was significant difference in the CMR results during the study especially in fourth group (SOF+DCV+RBV) group.

Conclusions: DAAs are proved its efficacy in management of chronic HCV in Egyptian patients as standard of care for hepatitis C treatment. Also tested its safety on the heart with most of its applied regimens.

Keywords: Hepatitis C virus, DAAS, Cardiovascular, Cardiac enzymes.

INTRODUCTION

Hepatitis C viral (HCV) infection is a major endemic medical problem in Egypt with higher prevalence rate worldwide [1, 2]. The prevalence rate of HCV in Egypt was reported as 14.7% in 2008 [3-5]. Infection rate was highly recorded in the Nile Delta and Upper Egypt with prevalence 26% and 28%, respectively [1].

HCV infection often causes extrahepatic diseases with innate immune and autoimmune pathogenic processes involved [6-10].

Hepatitis C virus (HCV) can be isolated from the myocardium of patients with myocarditis and cardiomyopathy and the mechanisms of damages the myocardium by the virus have not been elucidated [11-14].

Patients with advanced heart failure (HF) are mostly unable to tolerate interferon (IFN)-based anti-HCV therapies and had limited elimination efficacy [10].

The new direct-acting antiviral (DAA) agents are highly virus-specific and lack unspecific side-effects upon cardiac function which have always confounded the interpretation of IFN treatment data [15].

This interferon-free DAAs therapy considered as a successful hepatitis C treatment that can be offered to all patients irrespective of their co-morbidity [16, 17].

Recently, massive researches directed toward the improvement of direct acting antiviral agents (DAAs) able to hinder the action of viral enzymes worked to prohibit the HCV polyprotein processing and HCV replication. Alternative pathway is inactivation of the NS5A protein which affecting the replication of HCV.
and nonnucleoside inhibitors of the RNA-dependent polymerase [18].

To combat the development of resistance associated with VHC variants, combination of the first-generation NS3/4A protease inhibitors, boceprevir and telaprevir, and PEG-IFN and RBV [19] was used for the treatment of genotype 1, simprevir (second-generation NS3/4A protease inhibitor) with PEGIFN and RBV was approved for 12 weeks after the surgery [20].

Simprevir combined with PEG-IFN and RBV for 84 days and then replaced by combination of (PEG-IFN and RBV) for 3 to 12 months achieved sustained virological response (SVR) of 80% to 81% [21-23]. Sofosbuvir (SOF) as a nucleotide NS5B polymerase inhibitors was developed due to cross-resistance by 1st generation and 2nd generation protease inhibitors. Combination of SOF, PEG-IFN and RBV in genotype 1 (G1) for 3 months achieved sustained virological response (SVR) of 89% to 91% and was efficient for infection with genotype 4 (G4) [24].

The restricted protectively and tolerance of interferon-based treatments promote evolution of interferon-free treatments that show high efficacy, safety and of low cost as alternative medication [25]. SVR could be accomplished by an interferon free treatment [25, 26]. Sofosbuvir combined with RBV was applied for 12 weeks and 24 weeks in G2 and in G3, respectively. The use of SOF and RBV combination in G2 treatment-naive patients for 12 weeks achieved sustained virological response (SVR) of 92% - 97% and 94% - 100%, in non-cirrhotic and in cirrhotic, respectively in various experiments as Fission [27]. Positron, and Valence [28], various sofosbuvir medication showed promising efficacy when merged with another DAA [29].

This study was carried out to evaluate the effect of drug combinations without representing any cardiac complications including left ventricular (LV) dysfunction, significant arrhythmias, congestive heart failure and/or ACS.

**Material and Methods**

**Patients and Methods**

In this study, 390 patients diagnosed with chronic HCV infection, recruited in October 2016 to June 2017 in the virology clinics at Medical Specialized Hospital, Mansoura University, Egypt.

The current design comprise patients who suffering from chronic HCV infection and receiving gathering treatment. Patients were divided into 4 groups based on their direct acting antiviral agents (DAAS) regimens. Group A includes patients received ledipasvir and sofosbuvir (LED + SOF) for 12 weeks. Group B includes patients received simprevir and sofosbuvir (SIM+SOF) for 12 weeks. Group C includes patients received sofosbuvir and daclatasvir (SOF+DCV) for 12 weeks. Group D includes patients received sofosbuvir, daclatasvir and ribavirin (SOF+DCV + RBV) for 12 weeks.

The patients suffering from subsequent defined characters were eliminated; progressed liver cirrhosis, auto-immune hepatitis, advanced hepatitis B, both HBV and HVC, renal failure, ultimate thyroid problems, previous history of cardiac diseases, severe psychiatric disorders, diabetes mellitus, hypertension and/or Pregnancy.

All patients were assessed before starting treatment, one month after and 6 months after ending treatment. All participants accomplished a written informed consent. The local ethics committee was reviewed and approved the study protocol. All participated patients were checked for premature coronary artery by a cardiac assessment and case history.

**Ethical statement**

Medical Ethics research Committee at faculty of medicine, Mansoura University, Egypt was approved the study protocol. The participants in the current study were informed and assign the written consent. Confidentiality and personal privacy was admired in all procedures of the research. Obtained results and investigations will not be mentioned for any other objectives.

**Laboratory assessment of the patients**

The laboratory investigation of liver function enzymes including aspartate-aminotransferase (AST), alanine-aminotransferase (ALT), serum-bilirubin, serum-albumin, prothrombin time and international normalized ratio were performed for all participated patients.

Hematological investigation including serum creatinine, blood glucose level and complete blood picture was performed.

Thyroid-stimulating hormone, T3, T4, autoantibodies, antinuclear antibody and alpha fetoprotein were determined using Enzyme-linked immunosorbent assay (ELISA) protocol.

Cardiac enzymes (troponin I, creatine phosphokinase MB and β natriuretic peptide) were evaluated before starting treatment, during follow up and after 6 months of treatment.

**Clinical investigations**

The internal abdominal organs and kidneys were investigated for any abnormalities clinically and by using ultrasound tools.

The heart’s conduction system was assessed for the presence of arrhythmias and ST-T wave changes using a standard 12-lead Electrocardiogram (ECG) before the medication process and at the follow-up visit.

Cardiac MRI (CMR) was done before starting treatment, during follow up and after 6 months of treatment for assessment of the cardiac muscles state based on Lake Louis criteria for myocarditis in CMR.

**Statistical analysis**

The data were evaluated using IBM SPSS software package version 20.0. Quantitative results were assessed using mean, standard deviation for parametric results and median (range) for non-parametric variables after testing normality using Kolmogrov-Smirnov test. Significance of the gained results was calculated at the 5% level. One Way ANOVA test for parametric quantitative variables to compare between more than two studied groups with post Hoc LSD for pairwise comparison. Kruskal Wallis test for non-parametric quantitative variables, to compare between more than two studied groups with Mann Whitney U test for pairwise comparison. Qualitative variables were described as number and percentage with Chi-Square test for comparison and Monte Carlo test when higher than 20% of cells have count less than 5.

**Results**

The participated patients were studied regarding their pretreatment assessment including their laboratory investigations (liver functions, CBC, HCV RNA and serum creatinine), radiological investigations (abdominal ultrasound, CMR) and the level of cardiac enzymes before, during and after treatment with the required regimen of DAAS.

There was significant elevation in levels of AST, ALT, serum albumin, platelet count, hemoglobin concentration and the Child classification between the studied groups (Table 1).
Table 1: Comparison of laboratory results between studied groups

| Parameter        | LED + SOF (N=87) | SIM + SOF (N=60) | Sof + DCV (N=150) | SOF + DCV + RBV (N=93) | test of significance |
|------------------|------------------|------------------|-------------------|------------------------|---------------------|
| AST              | 38.0 (10.0-189.0) | 38.3 (10.0-189.0) | 32.00 (12.0-260.0) | 38.00 (17.0-310.0)     | KW P=0.049*         |
| ALT              | 36.00 (12.0-166.0) | 38.3 (8.0-166.0)  | 35.00 (12.0-160.0) | 41.00 (13.0-187.0)     | KW P=0.03*          |
| Total bilirubin  | 0.9 (0.3-4.0)    | 0.9 (0.3-2.6)    | 0.90 (0.3-4.0)    | 1.00 (0.3-4.0)         | KW P=0.06          |
| Platelet         | 141.0±30 (63.0-333.0) | 164.5±8 (65.0-492.0) | 158.0±8 (63.0-349.0) | 158.0±8 (78.0-349.0)   | KW P=0.004*        |
| HCV RNA*10⁴      | 150.98 (1.38-3110.0) | 212.0 (1.8-3947.8) | 262.0 (1.03-4386.2) | 135.9 (4.58-3803.9)    | KW P=0.6          |
| AFP              | 4.8 (1.0-40.0)   | 5.6 (1.0-56.0)   | 4.95 (1.0-95.13)  | 5.0 (1.0-67.0)         | KW P=0.4          |
| Albumin*         | 4.12±0.63       | 3.79±0.48        | 4.05±0.54         | 3.88±0.55             | F=5.99 P=0.001*    |
| INR              | 1.16±0.17       | 1.17±0.17        | 1.14±0.14         | 1.16±0.17            | F=1.2 P=0.31     |
| Child score      | 5                | 72 (82.8%)*      | 30 (50.0%)*       | 123 (82.0%)*           | MC P<0.001*      |
| 6                | 9 (10.3%)        | 21 (35.0%)       | 21 (14.0%)        | 15 (16.1%)            |                  |
| 7                | 3 (3.4%)         | 6 (10.0%)        | 3 (2.0%)          | 3 (3.2%)              |                  |
| 8                | 3 (3.4%)         | 3 (5.0%)         | 3 (2.0%)          | 6 (6.5%)              |                  |
| Creatinine       | 0.83±0.17       | 0.85±0.16        | 0.86±0.22         | 0.89±0.23             | F=1.42 P=0.237   |
| WBCS*            | 5.5±1.6         | 6.05±2.2         | 5.9±1.8           | 6.49±1.8              | F=4.43 P=0.004*   |
| HB*              | 13.12±1.98      | 13.04±1.6        | 11.93±1.94        | 12.06±2.2             | F=9.9 P<0.001*   |

Table 1: Comparison of laboratory results between studied groups

- All parameters described as median [Min-Max] except those marked * described as mean ± SD
- KW: Kruskal Wallis test
- F: One Way ANOVA test
- x²: Chi-square test
- p: probability
- *statistically significant difference at (p<0.05)
- Similar superscripted letters denote significant difference within same row

Table 2: Comparison of abdominal ultrasound findings results between studied groups

| Parameter                  | LED + SOF (N=87) | SIM + SOF (N=60) | Sof + DCV (N=150) | SOF + DCV+ RBV (N=93) | test of significance |
|----------------------------|------------------|------------------|-------------------|-----------------------|---------------------|
| Liver mean ± SD            | 2.38±0.85        | 2.0±0.63         | 2.29±0.69         | 2.35±0.48             | F=4.39 P<0.005*     |
| Spleen mean ± SD           | 1.48±0.5         | 1.4±0.6          | 1.52±0.50         | 1.0±0.7               | F=17.4 P<0.001*     |
| Absence of Focal lesion    | 87 (100.0%)      | 60 (100.0%)      | 243 (100.0%)      | 93 (100.0%)           |                    |

Table 2: Comparison of abdominal ultrasound findings results between studied groups

- F: One Way ANOVA test
- p: probability
- *statistically significant difference at (p<0.05)

There was significant difference in the CMR results during the study including mainly edema, early gadolinium enhancement (EGE), late gadolinium enhancement (LGE), LV dysfunction specially in 4th group (SOF+DCV+RBV) group. While, there was no statistical difference as regard pericardial effusion between the studied groups (Table 3).

Table 3: Comparison of CMR results between studied groups

| Parameter               | LED + SOF (N=87) | SIM + SOF (N=60) | Sof + DCV (N=150) | SOF + DCV+ RBV (N=93) | test of significance |
|-------------------------|------------------|------------------|-------------------|-----------------------|---------------------|
| Edema                   | 12 (13.8%)       | 12 (20.0%)       | 15 (10.0%)        | 27 (29.0%)            | MC P=0.002*         |
| EGE                     | 10 (11.5%)       | 12 (20.0%)       | 15 (10.0%)        | 27 (29.0%)            | MC P=0.001*         |
| LGE                     | 3 (3.4%)         | 2 (3.3%)         | 8 (5.3%)          | 24 (25.8%)            | MC P=0.001*         |
| LV dysfunction          | 3 (3.4%)         | 1 (1.7%)         | 3 (2.0%)          | 3 (2.0%)              | MC P=0.79           |

Table 3: Comparison of CMR results between studied groups

- MC: Monte Carlo test
- p: probability
- *statistically significant (P<0.05)
- Similar superscripted letters denote significant difference within same row.

Regarding to the cardiac enzymes (Troponin, CK MB, BNP ) analysis, there was significant elevation of them mostly in all groups especially in the fourth group (SOF+DCV+ RBV) with one outlier in SOF+DCV group and 3 outliers presented mainly with BNP (P value <0.001) (Table 4; Figure 1).
Table 4: Comparison of cardiac enzymes results between studied groups

| Criteria     | LED + SOF (N=87) | SIM + SOF N=60 | Sof + DCV (N=150) | SOF + DCV + RBV (N=93) | test of significance |
|--------------|------------------|----------------|--------------------|------------------------|---------------------|
|              | Median (Min-Max) | Median (Min-Max) | Median (Min-Max) | Median (Min-Max) | KW P=0.001* |
| BNP          | 60.0* (12.0-162.0) | 60.0* (12.0-210.0) | 56.0* (11.0-290.0) | 94.0* (11.0-370.0) |                    |
| Trop         | 0.5* (0.1-1.7)   | 0.5* (0.1-1.9)   | 0.5* (0.1-1.8)   | 0.5*AC (0.0-2.0)   | KW P=0.007*        |
| CK MB        | 1.0* (5.5-6.5)   | 1.5* (0.5-6.5)   | 1.8* (0.0-10.3)  | 2.0*AC (0.5-13.0)  | KW P=0.02*         |

- *statistically significant (P<0.05)
- Similar superscripted letters denote significant difference within same row.


toxicology caused by LDV/SOF may be attributed to other HCV DAATs. Cardio-toxicity was confirmed in HCV nucleotide-
polymerase-inhibitor and HCV NS3 inhibitors. Cardio-toxicity was not noticed in LDV/SOF experiment when the participant with significant cardiac co-morbidity were eliminated and without ECG disorders. In the previous report, 75% of USA Population suffering from HCV are in the age demographic with the highest prevalence of cardiovascular disease. The massive profit of LDV/SOF’s achieving sustained virology response (SVR) is an inconceivable disconnection in HCV medication.

In the second group treated with (SIM+SOF), there was significant difference in EGE, LGE and LV dysfunction with significant elevation in troponin levels in this group compared with the baseline. A previous study showed the manifestation of cardiac-toxic disorder correlated to the use of DAAs as a medication of chronic HCV. Medication using BMS-986094 with DCV and RBV was terminated after 34 patient’s experienced rapidly progressive heart failure and cardiac-toxicity were later identified. While a complete safety for the same regimen in the patient discovered HCV infection shortly after cardiac transplant was previously demonstrated. This schedule was used to reduce the involvement of the ongoing treatment, and especially the immune suppressive agents.

Regarding to the third and fourth group treated (SOF +DCV) and (SOF +DCV+RBV), respectively, there was significant elevation of CK-MB levels in the group treated with SOF+DCV, with increased edema, EGE,LGE when compared with the second group treated with (SIM + SOF).

In spite of safety of SOF+DCV regimen with or without ribavirin mentioned in many studies, sofosbuvir may cause potentially fatal heart arrhythmias. While, the prospect mode of action may be correlated to drug–drug interference of p-glycoprotein in cardiac myocytes or direct effect in the sino-atrial/atrioventricular node.

The current results considered of maximum clinical potency that DAAs are becoming the significant for hepatitis C medication. The patients exposed to sofosbuvir is supposed to elevated in a proportion that exceeds the number of patients included in the clinical experiment. Interestingly, the possibility of a small absolute risk increase is not excluded by the current evaluation, thus phase IV trials with longer follow-up or prolonged observational studies or registries (such as the Gilead Sustained Virologic Response Registry—ClinicalTrials.gov identifier NCT01457755) may participate more durable data to the evaluation of cardiac risks related to DAAs, especially sofosbuvir, as they may able to possess more of these seldom counter actions.

CONCLUSION

New HCV treatment with directly acting antiviral agents proved not only its efficacy in management of chronic HCV in Egyptian patients but also proved its safety on the heart with most of its applied regimens.

Although, in some regimens including semiprivar or daclatasvir, some patients show different degrees of cardiomyopathy, proved by elevation of cardiac enzymes and presence of edema in CMR, these


determined presence of myocarditis during the treatment which resolves after stopping the treatment. These findings was in agreement with previous report confirming that the patient developed myocarditis after starting the treatment with reduction in the LV EF and in RV systolic function.

The limited effect and constant side effects of Pegylated interferon (PEG-IFN) and ribavirin (RBV) which frequently used for HCV treatment, promote a development better alternative. In the last few years, a promising new direct-acting antiviral agents (DAAs) were developed and used for patients with chronic HCV and cirrhosis due to their increased efficacy, safety, and tolerability.

In the current study, the effect of four different DAAS treatment regime of HCV infection was evaluated and their effect on potential cardiac toxicity focusing on cardiac muscles affection was assessed.

In the first group treated with (LED + SOF), there was elevation of the cardiac enzymes especially BNP constant with edema of the cardiac muscles in CMR denoting presence of myocarditis during the treatment which resolves after stopping the treatment. These findings was in agreement with previous report confirming that the patient developed myocarditis after starting the treatment with reduction in the LV EF and in RV systolic function.

The cardio-toxicity caused by LDV/SOF may be attributed to other HCV DAATs. Cardio-toxicity was confirmed in HCV nucleotide-polymerase-inhibitor and HCV NS3 inhibitors. Cardio-toxicity was not noticed in LDV/SOF experiment when the participant with significant cardiac co-morbidity were eliminated and without ECG disorders. In the previous report, 75% of USA Population suffering from HCV are in the age demographic with the highest prevalence of cardiovascular disease. The massive profit of LDV/SOF’s achieving sustained virology response (SVR) is an inconceivable disconnection in HCV medication.

In the second group treated with (SIM+SOF), there was significant difference in EGE, LGE and LV dysfunction with significant elevation in troponin levels in this group compared with the baseline. A previous study showed the manifestation of cardiac-toxic disorder correlated to the use of DAAs as a medication of chronic HCV. Medication using BMS-986094 with DCV and RBV was terminated after 34 patient’s experienced rapidly progressive heart failure and cardiac-toxicity were later identified. While a complete safety for the same regimen in the patient discovered HCV infection shortly after cardiac transplant was previously demonstrated. This schedule was used to reduce the involvement of the ongoing treatment, and especially the immune suppressive agents.

Regarding to the third and fourth group treated (SOF +DCV) and (SOF +DCV+RBV), respectively, there was significant elevation of CK-MB levels in the group treated with SOF+DCV, with increased edema, EGE,LGE when compared with the second group treated with (SIM + SOF).

In spite of safety of SOF+DCV regimen with or without ribavirin mentioned in many studies, sofosbuvir may cause potentially fatal heart arrhythmias. While, the prospect mode of action may be correlated to drug–drug interference of p-glycoprotein in cardiac myocytes or direct effect in the sino-atrial/atrioventricular node.

The current results considered of maximum clinical potency that DAAs are becoming the significant for hepatitis C medication. The patients exposed to sofosbuvir is supposed to elevated in a proportion that exceeds the number of patients included in the clinical experiment. Interestingly, the possibility of a small absolute risk increase is not excluded by the current evaluation, thus phase IV trials with longer follow-up or prolonged observational studies or registries (such as the Gilead Sustained Virologic Response Registry—ClinicalTrials.gov identifier NCT01457755) may participate more durable data to the evaluation of cardiac risks related to DAAs, especially sofosbuvir, as they may able to possess more of these seldom counter actions.

CONCLUSION

New HCV treatment with directly acting antiviral agents proved not only its efficacy in management of chronic HCV in Egyptian patients but also proved its safety on the heart with most of its applied regimens.

Although, in some regimens including semiprivar or daclatasvir, some patients show different degrees of cardiomyopathy, proved by elevation of cardiac enzymes and presence of edema in CMR, these
changes was reversible after stoppage of treatment without leaving any permanent cardiac damage.

Acknowledgment

The authors expressed their sincere gratitude to the participant in this study. Great acknowledgment directed to technicians and assistants at Mansoura Specialized Medical Hospital, Mansoura University, Egypt for their excellent technical support.

Funding: Not applicable.

Disclosure: The authors have no conflict of interest to declare.

REFERENCES

1. Elgharably A, Gomaa A, Crosse M, Norsworthy P, Waked I, Taylor-Robinson S. Hepatitis C in Egypt – past, present, and future. Int J General Med 2017; 10:1-6.
2. Shepherd C, Finelli L, Alter M. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 2005; 5(9):558-567.
3. Amer F, Gohar M, Yousif M. Epidemiology of hepatitis C virus infection in Egypt. Int J Trop Dis 2015; 73:119-131.
4. Petti S, Maida M, Macaluso F, et al. Hepatitis C virus infection is associated with increased cardiovascular mortality: A meta-analysis of observational studies. Gastroenterol 2016; 150(1):145-155.e144; quiz e115-146.
5. Voulgaris T, Sevastianos V. Atherosclerosis as extrahepatic manifestation of chronic infection with hepatitis C virus. Hepat Res Treat 2016; 2016:8.
6. Bang B, Elmasry S, Saito T. Organ system view of chronic infection with hepatitis C virus. Hepat Res Treat 2016; 9:150(1):145-155.e144; quiz e115-146.
7. Voulgaris T, Sevastianos V. Atherosclerosis as extrahepatic manifestation of chronic infection with hepatitis C virus. Hepat Res Treat 2016; 2016:8.
8. Bang B, Elmasry S, Saito T. Organ system view of the hepatic innate immunity in HCV infection. J Med Virol 2016; 88(12):2025-2037.
9. Galli F, Basile U, Gragnani L, et al. Autoimmunity and lymphoproliferation markers in naive HCV-RNA positive patients without clinical evidences of autoimmune/lymphoproliferative disorders. Dig Liver Dis 2016; 48(8):927-933.
10. Narciso-Chiavon J, Schiavon L. Autoantibodies in chronic hepatitis C: A clinical perspective. World J Hepatol 2015; 7(8):1074-1085.
11. Zignego A, Gragnani L, Piluso A, et al. Virus-driven autoimmunity and lymphoproliferation: the example of HCV infection. Expert review of clinical immunology 2015; 11(1):15-31.
12. Poller W, Kaya Z, Muche M, et al. High incidence of cardiac dysfunction and response to antiviral treatment in patients with chronic hepatitis C virus infection. Clin Res Cardiol 2017; 106(7):551-556.
13. Sanchez M, Bergasa N. Hepatitis C associated cardiomyopathy: potential pathogenic mechanisms and clinical implications. Med Sci Monit 2008; 14(S):Ra55-63.
14. Boyella V, Onyebueke I, Farraj N, Graham-Hill S, El Younis C, Bergasa NV. Prevalence of hepatitis C virus infection in patients with cardiomyopathy. Ann Hepatol. 2009; 8(2):113-115.
15. Matsumori A. Hepatitis C virus infection and cardiomyopathies. Circ Res 2009; 96(2):144-147.
16. Omura T, Yoshiyama M, Hayashi T, et al. Core protein of hepatitis C virus induces cardiomyopathy. Circ Res 2005; 96(2):148-150.
17. Poller W, Haghioka A, Kasner M, et al. Cardiovascular involvement in chronic hepatitis C virus infections – Insight from novel antiviral therapies. J Clin Trans Hepatol, 2018.
18. Spengler U. Direct antiviral agents (DAAs) - A new age in the treatment of hepatitis C virus infection. Pharmacol Ther 2018; 183:118-126.
19. Jennifer J, Charles F. Direct-Acting Antiviral Agents for hepatitis C virus infection. Ann Rev Pharmacol Toxicol 2013; 53(1):427-449.
20. Cholongitas E, Papatheodoridis G. Review article: novel therapeutic options for chronic hepatitis C. Aliment Pharmacol Ther 2008; 27(10):866-884.
21. Kwo P, Lawitz EJ, Mccone J, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2a and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. Lancet 2010: 376(9742):705-716.
22. Jacobson I, Dore G, Foster G, et al. 1425 Simeprevir (TMC435) with peginterferon/ribavirin for chronic HCV genotype-1 infection in treatment-naive patients: results from Quest-1, a phase III trial. J Hepatol 2013; 58:5574.
23. Fried M, Buti M, Dore G, et al. Once-daily simeprevir (TMC435) with pegylated interferon and ribavirin in treatment-naive genotype 1 hepatitis C: the randomized PILLAR study. Hepatol 2013; 58(6):1918-1929.