Evaluation of fibrosis in chronic hepatitis C patients treated with direct-acting antivirals

Ayse Goken Tufan1, Gozde Dervis Hakim2, Harun Akar3, Mesut Akarsu3

1Department of Internal Medicine, Izmir Tepecik Training and Research Hospital, Izmir, Turkey; 2Department of Gastroenterology, Izmir Tepecik Training and Research Hospital, Izmir, Turkey; 3Department of Gastroenterology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey

Abstract

Background and Aim: This study is an evaluation of liver fibrosis measurements determined using transient elastography and aspartate aminotransferase-to-platelet ratio index (APRI) scores of patients diagnosed with chronic hepatitis C (CHC) who were treated with direct-acting antivirals (DAAs).

Materials and Methods: The liver fibrosis measurements recorded using transient elastography, APRI scores, and the biochemical data from before and after treatment of 40 patients with CHC who were treated with DAA were reviewed. Patients who received paritaprevir+ritonavir/ombitasvir+dasabuvir were included in Group 1 (n=20), and patients who received sofosbuvir+ledipasvir+ribavirin in Group 2 (n=20).

Results: The mean liver fibrosis measurement of the patients was 15.73±10.63 kPa (min–max: 5.20–45.00 kPa) before treatment and 2.56±8.84 kPa (min–max: 4.30–42.00 kPa) after treatment. There was a significant improvement in liver fibrosis with a regression of 20.16% at the end of treatment compared with the start (p=0.001) with no significant difference between treatment groups (p=0.542). The highest regression rate of 75% was seen in patients with F2 fibrosis at the end of treatment. Significant regression was also found in patients with F3 fibrosis, with a rate of 57.2%, and in those with F4 fibrosis, with a rate of 17.6% (p=0.035). Significant reduction was also observed in the APRI scores of patients at the end of treatment compared with the start of treatment (p=0.001), with no significant difference between treatment groups (p=0.328).

Conclusion: Noninvasive assessments of CHC patients treated with DAA revealed regression in liver fibrosis measurements and APRI scores and significant improvements were seen in the stage of fibrosis in the early phases following treatment.

Keywords: Direct acting antivirals; fibroscan; hepatitis C.

Introduction

Hepatitis C virus (HCV) is an important cause of chronic liver disease that infects 130–150 million people worldwide with a prevalence of 2–3%. It has been established that worldwide, some 350,000 patients per year lose their lives due to HIV infection. Spontaneous clearance of HCV within six weeks following acute hepatitis C infection occurs in only 15–25% of the patients, and chronic hepatitis and fibrosis develop in the majority of patients. Structural changes of the parenchyma resulting from progression of the fibrosis are accompanied by clinical manifestations of chronic liver disease and hepatic dysfunction. The onset of liver fibrosis is usually insidious, and mortality and morbidity are associated with cirrhosis usually developing 20–30 years later. The stage of liver fibrosis is associated with prognosis in chronic hepatitis C (CHC) infection; it has an important effect on treatment strategy and follow-up. A liver biopsy is currently regarded as the gold standard procedure for the assessment of fibrosis; however, it is an invasive procedure with serious complications in rare conditions, there may be discrepancies between observers, and sampling errors may occur. It is difficult to monitor the dynamic process of progressive and regressive liver fibrosis with repeated liver biopsies, as it is not easily tolerated by the patients. These limitations to the use of a liver biopsy led to the need for a reliable, repeatable, noninvasive method for evaluating liver fibrosis.

Transient elastography (TE) uses a device that quantitatively measures liver fibrosis and is regarded as an important tool in the evaluation, follow-up, and treatment of fibrosis in chronic liver disorders. The combined use of serum markers and TE is known to increase the accuracy in the diagnosis of fibrosis. The most effective approach recommended in the current guidelines for the evaluation of severity and fibrosis of liver disease is the combination of direct biological markers and TE. A biopsy is recommended for any patient with discrepancies between the first two methods when those results affecting clinical decision-making, and it has been reported that the need for a liver biopsy can be markedly decreased with this approach.

The aim of this study was to evaluate the changes in fibrosis occurring after treatment with noninvasive methods by analyzing liver fibrosis measurements obtained with TE and aspartate aminotransferase (AST)-to-platelet ratio index (APRI) scores in CHC patients treated with direct-acting antivirals (DAA).

Materials and Methods

Patients

Forty CHC patients followed at Tepecik Training and Research Hospital Department of Gastroenterology who had completed a treatment regimen with DAA and who had undergone liver fibrosis measurements with a Fibroscan 502 Touch (Echosens, Paris, France) before and after treatment and at 12 and 24 weeks were included in the study. The patients were evaluated in 2 groups: those receiving paritaprevir+ritonavir/ombitasvir+dasabuvir treatment were assigned to Group 1 (n=20), and those receiving sofosbuvir+ledipasvir+ribavirin to Group 2 (n=20). Patients included in the study provided written, informed consent.
HCV-RNA was undetectable in all of the patients included in the study (n=40) at the end of treatment. The sustained virological response (SVR) 12 weeks after treatment (SVR12) and/or 24 weeks (SVR24) after the end of treatment are conventionally used as CHC therapy endpoints. Approval for this study was obtained from the Ethics Committee of Clinical and Laboratory Research of Tepecik Training and Research Hospital (no: 2017/13-1).

Data Collection
Details of age, gender, HCV genotype, cirrhosis status, and previous treatment for HCV of all of the patients included in the study were recorded. AST, alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), total bilirubin, international normalized ratio (INR), serum creatinine, white blood cell (WBC), hemoglobin, and platelet data before and after treatment with DAA were retrospectively reviewed and noted. Liver fibrosis measurements obtained with the Fibroscan device and APRI scores from before and after treatment were also retrospectively reviewed and recorded.

Non-invasive Tests
APRI scores were calculated using the Wai formula:[14] (AST/upper limit of normal)/platelet count (expressed as platelets x 10^9/L) x 100
The fibrosis stage cut-off values for APRI scores were:[14] mild/no fibrosis (F0-1), APRI<0.5; significant fibrosis (F2-3), APRI=0.5–1.9; cirrhosis (F4), APRI≥2.
The liver fibrosis measurements were performed by a single experienced operator using the Fibroscan device and an M-probe. The measurements were expressed as kPa and the mean value of 10 measurements taken at a depth of 25–65 mm was recorded. Measurements with a success rate (successful measurements >100/all measurements) of at least 60% and an interquartile range/M ratio of less than 30% were considered valid and used for statistical analysis. The cut-off values for the liver fibrosis measurements according to the Metavir fibrosis stages were as follows:[14] F0-1: 2.5–7 kPA, F2: 7.1–9.5 kPA, F3: 9.5–12.5 kPA, F4: >12.5 kPA.

Statistical Analyses
All of the study data were analyzed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA) Numerical variables were first tested for normality with the Shapiro-Wilk test. Normality was achieved for data that did not conform to normal distribution by applying log transformation. Variables that did not conform to normality with log transformation were analyzed using non-parametric tests.
Analysis of variance with repeated measures was carried out in patients before and after treatment. Pre- and post-treatment analyses of all of the patients were conducted using a paired groups t-test without taking the group into consideration. Cross tabulation was performed on categorical data, and chi-square and McNemar tests were used for analysis. Analysis of triple fibrosis scoring for APRI values was performed with Wilcoxon paired groups testing in each patient group.
For numerical variables, Pearson’s correlation coefficient was calculated for those conforming to normal distribution, and Spearman’s rho correlation coefficient for those not conforming to normal distribution. The level of statistical significance was a p value <0.05.

Table 1. Demographic data of the patients

| Characteristics | Total patients (n=40) | Group 1 (n=20) | Group 2 (n=20) | p   |
|-----------------|----------------------|---------------|---------------|-----|
| Age (years) (mean) | 62.53±12.82         | 61.75±10.49   | 63.30±15.04   | 0.708|
| Male            | 14 35               | 9 45          | 5 25          | 0.185|
| Female          | 26 65               | 11 55         | 15 75         |       |
| Treatment naive | 24 60               | 14 70         | 10 50         | 0.197|
| Non-treatment naive | 16 40           | 6 30          | 10 50         |       |
| Mean BMI (kg/m²) | 27.18±4.41          | 27.03±4.95    | 27.33±3.92    | 0.836|
| BMI (normal) (kg/m²) | 11 27.5         | 6 30          | 5 25          |       |
| BMI (overweight) (kg/m²) | 21 52.5        | 10 50         | 11 55         | 0.933|
| BMI (obese) (kg/m²) | 8 20             | 4 20          | 4 20          |       |

BMI: Body mass index.

Hepatology Forum 2020 Vol. 2 | 53–58
Biochemical Findings

The mean AST, ALT, GGT, bilirubin, INR, creatinine, WBC, hemoglobin, and platelet values of the patients before and after treatment are provided in Table 2.

There was a significant reduction in AST (p<0.001), ALT (p=0.001), and GGT (p<0.001) values following treatment with no significant difference between the groups. Significant changes were not seen in serum bilirubin, creatinine, or INR values following treatment, again without significant difference between the treatment groups.

The mean pre- and post-treatment WBC value of the patients was 6.87±2.56 10³/µL and 7.11±2.58 10³/µL, respectively. A mild elevation was noted following treatment; however, this change was not statistically significant (p=0.383).

Liver Fibrosis Measurements

The mean liver fibrosis measurement was 15.73±10.63 kPa (min–max: 5.20–45.00 kPa) at the end of treatment; a reduction of 4.30% (mean difference: -3.17±5.83 kPa) was noted and the reduction following treatment was found to be significant (p<0.001). The liver fibrosis measurement values of the two groups were statistically similar before and after treatment (p=0.236). The mean pre- and post-treatment platelet count was 195.15±85.48 10³/µL and 202.38±79.86 10³/µL, respectively. An elevation was noted in platelet counts following treatment but it was not statistically significant (p=0.219). There were mild increases in the platelet count in both groups following treatment, but without a significant difference between the groups (p=0.956).

APRI Scores

The mean pre- and post-treatment APRI score was 0.90±0.79 and 0.39±0.29, respectively, and a significant decrease was noted in the APRI score following treatment (p<0.001). The pre- and post-treatment APRI scores were statistically comparable between the groups (p=0.328). The APRI scores before treatment indicated that 15 of the 40 patients (37.5%) had F0-1 fibrosis, 20 (50%) had F2-3, and 5 (12.5%) had F4 fibrosis. When the patients were distributed in terms of the APRI score following treatment, all 5 patients who had F4 fibrosis before treatment (100%) had regressed to F2-3 fibrosis, 14 of 20 patients who had F2-3 fibrosis (70%) had regressed to F0-1, and 6 patients (30%) remained at F2-3 stage. The regression in fibrosis at the end of treatment according to the APRI score was statistically significant (p<0.01) (Table 3).

The APRI score showed a positive correlation with AST, ALT, total bilirubin, INR, and a negative correlation with WBC and platelet counts (Table 4).
Most of the patients infected with HCV, in many studies with long-term follow-up, have developed a chronic infection and, if left untreated, approximately 30% of the patients will progress to cirrhosis in 20–30 years. On the other hand, successful antiviral treatment and achieving SVR reduces liver-related morbidity and mortality, HCC incidence, and the need for liver transplantation.17,18 The reported SVR rate is 50–55% in all genotypes with regimens containing pegylated interferon and ribavirin; however, the SVR rate has notably reached 99% with currently available regimens containing DAA.19

Numerous serological, biochemical indicator, and imaging methods have been developed to evaluate liver fibrosis noninvasively.20 Among the frequently administered noninvasive methods, APRI, an indirect biochemical indicator, has been validated in studies performed on patients with CHC, and is one of the simple panels that can diagnose marked fibrosis and cirrhosis with acceptable accuracy.21 Another method to evaluate liver fibrosis noninvasively is TE. TE with FibroScan is a reliable, noninvasive, and repeatable assessment technique that can measure liver fibrosis and evaluate large amounts of liver tissue.22 Current guidelines for the management of HCV infection recommend that the most effective approach to the evaluation of the severity of liver disease and fibrosis is combining direct biochemical indicators with the use of TE.21,23 A biopsy is recommended for any patient when there are discrepancies between these two methods with results that could affect clinical decision-making. It is thought that need to perform a liver biopsy can be markedly reduced with this approach.

While liver fibrosis was once regarded as an irreversible progression, it is now known to be a dynamic process as a result of recent evidence demonstrating regression and variability.23 In many studies with long-term follow-up of fibrosis in patients with CHC, a marked decrease has been noted in liver fibrosis values in patients achieving SVR with antivirals compared with those unresponsive to treatment.24

In 2017, Gheorghe et al.25 reported on 681 compensated cirrhotic patients with CHC and genotype 1b who had received a 12-week DAA (ombitasvir/paritaprevir/ritonavir/daclatasvir) treatment. Liver fibrosis was measured before treatment, at the end of treatment, and in the third month after treatment (SVR12). A significant improvement was observed in the third month after treatment compared with the baseline measurement of liver fibrosis.

Table 4. Comparison of APRI scores with other parameters

|                  | r     | p      |
|------------------|-------|--------|
| APRI versus AST  | 0.766 | <0.001 |
| APRI versus ALT  | 0.514 | 0.001  |
| APRI versus total bilirubin | 0.369 | 0.019  |
| APRI versus INR  | 0.678 | <0.001 |
| APRI versus WBC  | -0.485| 0.002  |
| APRI versus platelet count | -0.727| <0.001 |

APRI scores showed a positive correlation with AST, ALT, total bilirubin, and INR, and a negative correlation with WBC and platelet counts. ALT: Alanine aminotransferase; APRI: Aspartate aminotransferase-to-platelet ratio index; AST: Aspartate aminotransferase; INR: International normalized ratio; WBC: White blood cell.

Table 5. Fibrosis stage according to liver fibrosis measurements before and after treatment

| Liver fibrosis after treatment |
|------------------------------|
| All patients | F0-1 | F2 | F3 | F4 | Total |
| (n=40) | n | n | n | n | n | % |
| F0-1 (n) | 8 | 0 | 0 | 0 | 8 | 20 |
| F2 (n) | 6 | 1 | 0 | 1 | 8 | 20 |
| F3 (n) | 3 | 1 | 2 | 1 | 7 | 17.5 |
| F4 (n) | 0 | 0 | 3 | 14 | 17 | 42.5 |
| Total | n | 17 | 2 | 5 | 16 | 40 |
| % | 42.5 | 5 | 12.5 | 40 | 100 |

Table 6. Comparison of liver fibrosis measurements with other parameters

|                  | r     | p      |
|------------------|-------|--------|
| Liver stiffness versus AST | 0.512 | 0.001  |
| Liver stiffness versus ALT | 0.160 | 0.324  |
| Liver stiffness versus GGT | 0.079 | 0.626  |
| Liver stiffness versus total bilirubin | 0.140 | 0.931  |
| Liver stiffness versus INR | 0.318 | 0.045  |
| Liver stiffness versus serum creatinine | -0.189 | 0.244 |
| Liver stiffness versus WBC | 0.790 | 0.670  |
| Liver stiffness versus hemoglobin | -0.329 | 0.038  |
| Liver stiffness versus platelet count | -0.341 | 0.031  |
| Liver stiffness versus APRI | 0.483 | 0.002  |

Liver fibrosis measurements obtained using transient elastography demonstrated a powerful correlation with APRI and AST, a positive correlation with INR, and a negative correlation with hemoglobin and platelet counts. ALT: Alanine aminotransferase; APRI: Aspartate aminotransferase-to-platelet ratio index; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; INR: International normalized ratio; WBC: White blood cell.

When changes in fibrosis stage were analyzed according to the pre- and post-treatment measurements of liver fibrosis, it was noted that 20% of the patients (n=8) had F0-1 fibrosis, 20% (n=8) had F2 fibrosis, 17.5% (n=7) had F3 fibrosis, and 42.5% (n=17) had F4 fibrosis before treatment. Fourteen of 17 patients who had F4 fibrosis before DAA treatment (82.4%) remained at F4, while 3 patients (17.6%) regressed to F3 fibrosis. One of 7 patients who had F3 fibrosis before treatment (14.3%) progressed to F4 fibrosis, 1 patient (14.3%) regressed to F2 fibrosis and 3 patients (42.9%) regressed to F0-1 fibrosis. One of 8 patients who had F2 fibrosis before treatment (12.5%) progressed to F4 fibrosis, 1 patient (12.5%) maintained an F2 stage, and 6 patients (75%) regressed to F0-1 fibrosis. When the changes in fibrosis stage following antiviral treatment were evaluated in all of the patients according to the liver fibrosis measurements, a statistically significant regression was noted compared with the pre-treatment values (p=0.035) (Table 5). When the two groups were compared regarding changes in the degree of fibrosis, there was no significant difference between the groups (p=0.917).

The liver fibrosis measurements obtained with TE showed a powerful correlation with APRI and AST, a positive correlation with INR, and a negative correlation with hemoglobin and platelet counts (Table 6).

Discussion

End-stage liver disease due to CHC is currently a major cause of liver-related deaths worldwide.26 Most of the patients infected with HCV develop a chronic infection and if left untreated, approximately 30% of the patients will progress to cirrhosis in 20–30 years. On the other hand, successful antiviral treatment and achieving SVR reduces liver-related morbidity and mortality, HCC incidence, and the need for liver transplantation.17,18 The reported SVR rate is 50–55% in all genotypes with regimens containing pegylated interferon and ribavirin; however, the SVR rate has notably reached 99% with currently available regimens containing DAA.19

Numerous serological, biochemical indicator, and imaging methods have been developed to evaluate liver fibrosis noninvasively.20 Among the frequently administered noninvasive methods, APRI, an indirect biochemical indicator, has been validated in studies performed on patients with CHC, and is one of the simple panels that can diagnose marked fibrosis and cirrhosis with acceptable accuracy.21 Another method to evaluate liver fibrosis noninvasively is TE. TE with FibroScan is a reliable, noninvasive, and repeatable assessment technique that can measure liver fibrosis and evaluate large amounts of liver tissue.22 Current guidelines for the management of HCV infection recommend that the most effective approach to the evaluation of the severity of liver disease and fibrosis is combining direct biochemical indicators with the use of TE.21,23 A biopsy is recommended for any patient when there are discrepancies between these two methods with results that could affect clinical decision-making. It is thought that need to perform a liver biopsy can be markedly reduced with this approach.

While liver fibrosis was once regarded as an irreversible progression, it is now known to be a dynamic process as a result of recent evidence demonstrating regression and variability.23 In many studies with long-term follow-up of fibrosis in patients with CHC, a marked decrease has been noted in liver fibrosis values in patients achieving SVR with antivirals compared with those unresponsive to treatment.24 In 2017, Gheorghe et al.25 reported on 681 compensated cirrhotic patients with CHC and genotype 1b who had received a 12-week DAA (ombitasvir/paritaprevir/ritonavir/daclatasvir) treatment. Liver fibrosis was measured before treatment, at the end of treatment, and in the third month after treatment (SVR12). A significant improvement was observed in the third month after treatment compared with the baseline measurement of liver fibrosis.
Approval for this study was obtained from the Ethics Committee of Clinical and Laboratory Research of Tepecik Training and Research Hospital (date: 21.09.2017, number: 2017/13-1).

In our study, a significant regression was found in liver fibrosis measurements and APRI values in patients with CHC following treatment with current antiviral treatments and significant improvement was seen in fibrosis with antiviral treatment with DAAAs even at the early stage of following treatment. However, it should be kept in mind that patients who remain in the cirrhotic group after treatment, which was 40% of our study group, are still at risk for cirrhosis complications. A longer period of follow-up and measurements are needed particularly regarding fibrosis changes in patients with advanced fibrosis and cirrhosis. As an easy-to-use and a repeatable non-invasive method, TE and APRI can be useful tools in the evaluation of the dynamic process of fibrosis in CHC and in the prediction of complications due to chronic liver disease.

Acknowledgements: We would like to thank to Prof. Dr. Ulus Salih Akarca and TKAD Izmir for their support on use of fibroscan device.

Ethics Committee Approval: Approval for this study was obtained from the Ethics Committee of Clinical and Laboratory Research of Tepecik Training and Research Hospital (date: 21.09.2017, number: 2017/13-1).

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 2005;5(9):558-567.

2. Papatheodoridis G, Hatzakis A. Public health issues of hepatitis C virus infection. Best Pract Res Clin Gastroenterol 2012;26(4):371-380.
3. Myrmel H, Ulvestad E, Asjø B. The hepatitis C virus enigma. APMIS 2009;117(5-6):427-439.
4. Friedman SL. Mechanisms of hepatic fibrogenesis. Gastroenterology 2008;134(6):1655-1669.
5. Dranoff JA, Wells RG. Portal fibroblasts: Underappreciated mediators of biliary fibrosis. Hepatology 2010;51(4):1438-1444.
6. Afshal NH, Nunes D. Evaluation of liver fibrosis: a concise review. Am J Gastroenterol 2004;99(6):1160-1174.
7. Bataller R, Brenner DA. Liver fibrosis. J Clin Invest 2005;115(2):209-218.
8. Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pyrsopoulos NT, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol 2002;97(10):2614-2618.
9. Sheela H, Seela S, Caldwell C, Boyer JL, Jain D. Liver biopsy: evolving role in the new millennium. J Clin Gastroenterol 2005;39(7):603-610.
10. Sandrin L, Tanter M, Catheline S, Fink M. Shear modulus imaging with 2-D transient elastography. IEEE Trans Ultrason Ferroelectr Freq Control 2002;49(4):426-435.
11. Castéra L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology 2005;128(2):343-350.
12. American Association for the Study of Liver Diseases and Infectious Diseases Society of America. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. Accessed at: http://www.hcvguidelines.org.
13. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu. EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol 2017;66(1):153-194.
14. Lin ZH, Xin YN, Dong QJ, Wang Q, Jiang XJ, Zhan SH, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. Hepatology 2011;53(3):726-736.
15. Castera L, Forns X, Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. J Hepatol 2008;48(5):835-847.
16. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol 2006;45(4):529-538.
17. van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, Duarte-Rojo A, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA. 2012;308(24):2584-2593.
18. Morisco F, Granata R, Stroffolini T, Guarino M, Donnarumma L, Gaeta L, et al. Sustained virological response: a milestone in the treatment of chronic hepatitis C. World J Gastroenterol 2013;19(18):2793-2798.
19. A Special Meeting Review Edition: Advances in the Treatment of Hepatitis C Virus Infection From EASL 2015: The 50th Annual Meeting of the European Association for the Study of the Liver. April 22-26, 2015. Gastroenterol Hepatol (N Y) 2015;11(6 Suppl 3):1-23.
20. Sebastiani G, Alberti A. Non-invasive fibrosis biomarkers reduce but not substitute the need for liver biopsy. World J Gastroenterol 2006;12(23):3682-3694.
21. Ziol M, Handra-Luca A, Kettaneh A, Christidis C, Mal F, Kazemi F, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. Hepatology 2005;41(1):48-54.
22. Issa R, Williams E, Trim N, Kendall T, Arthur MJ, Reichen J, et al. Apoptosis of hepatic stellate cells: involvement in resolution of biliary fibrosis and regulation by soluble growth factors. Gut 2001;48(4):548-557.
23. Vergniol J, Foucher J, Castéra L, Bernard PH, Tournan R, Terrebonne E, et al. Changes of non-invasive markers and FibroScan values during HCV treatment. J Viral Hepat 2009;16(2):132-140.
24. Hézode C, Castéra L, Roulot-Thoraval F, Bouver-Caissier M, Rosa I, Roulot D, et al. Liver stiffness diminishes with antiviral response in chronic hepatitis C. Aliment Pharmacol Ther 2011;34(6):656-663.
25. Gheorghié L, Iacob S, Curescu M, Brise C, Cijevschi C, Caruntu F, et al. Real-Life Use of 3 Direct-Acting Antiviral Regimen in a Large Cohort of Patients with Genotype-1b HCV Compensated Cirrhosis. J Gastrointestin Liver Dis 2017;26(3):275-281.
26. Tag-Adeen M, Sabra AM, Akazawa Y, Ohnita K, Nakao K. Impact of hepatitis C virus genotype-4 eradication following direct acting antivirals on liver stiffness measurement. Hepat Med 2017;9:45-53.
27. Pons M, Santos B, Simón-Talero M, Ventura-Cots M, Riveiro-Barciela M, Esteban R, et al. Rapid liver and spleen stiffness improvement in compensated advanced chronic liver disease patients treated with oral antivirals. Therap Adv Gastroenterol 2017;10(8):619-629.
28. Bernuth S, Yagmur E, Schuppan D, Sprinzl MF, Zimmermann A, Schad A, et al. Early changes in dynamic biomarkers of liver fibrosis in hepatitis C virus-infected patients treated with sofosbuvir. Dig Liver Dis 2016;48(3):291-297.