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Inferior Outcomes after Late use of Direct-Acting Antiviral Agents in Patients with Recurrent Hepatitis C Infection after Liver Transplantation

Meng-Chuan Lu[1], Yi-Ting Chou[1], Jung-Chun Lin[1], Hsuan-Hwai Lin[1], Wei-Chen Huang[1], Hsiu-Lung Fan[2], Teng-Wei Chen[2], Chung-Bao Hsieh[2], Tsai-Yuan Hsieh[1] and Yu-Lueng Shih[1*]

[1]Division of Gastroenterology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

[2]Division of Organ Transplantation Surgery, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

[*]Corresponding author:

Yu-Lueng Shih,
Division of Gastroenterology, Department of Internal Medicine Department of Internal Medicine/ National Defense Medical Center / Tri-Service General Hospital, No 325, Section 2, Cheng-Kung Road, Taipei, Neihu 11490, Taiwan,
Tel: +886-2-87927409, Fax: +886-2-87927139,
E-mail: albreb@ms28.hinet.net

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Keywords:

Hepatitis C reinfection; Post operation; Period; FIB-4 score; Prognosis

Abbreviations:

AST: Aspartate Amino Transferase; ALT: Alanine Amino Transferase; CAD: Coronary Artery Disease; CKD: Chronic Kidney Disease; CT: Computed Tomography; DAA: Direct Acting Antiviral; DD: Deceased Donor; DLC: Decompensated Liver Cirrhosis; DM: Diabetic Mellitus; FIB-4; Fibrosis-4; GT: Genotype; HCC: Hepatocellular Carcinoma; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; HTN: Hypertension; LD: Living Donor; LT: Liver Transplantation; MELD: Model for End-Stage Liver Disease: NHI; National Health Insurance; PLT: Platelets; RNA: Ribonucleic Acid; SVR: Sustained Virologic Response

1. Abstract

1.1. Background

Recurrent hepatitis C virus (HCV) infection after liver transplantation results in subsequent accelerated fibrosis. However, the prognosis as it relates to the timing of direct-acting antiviral (DAA) treatment after liver transplantation has not been widely investigated.

1.2. Methods

A retrospective observational study was performed from October 2003 to September 2019, including 21 patients with recurrent HCV infection from one center who started DAA therapy after an interval that ranged from 1 to 71 months after liver transplantation. This study used the FIB-4 score as a treatment response marker and Spearman's correlation coefficient to evaluate the correlation between the interval and the FIB-4 score.

1.3. Results

A longer interval between liver transplantation and DAA initiation was correlated with a higher FIB-4 score, and the correlation coefficient became higher as the observation interval became longer.

1.4. Conclusions

The inferior prognosis of hepatic fibrosis was correlated with a longer period between surgery and initiation of DAA treatment, which may offer an important new method that can be used to evaluate the prognosis of patients who plan to be treated with DAA, especially for patients with undetectable HCV RNA in the early stage, those who are intolerant to interferon therapy, and those without regular outpatient monitoring.

2. Introduction

Chronic hepatitis C infection is a leading cause of end-stage liver disease worldwide, and along with hepatocellular carcinoma and hepatic failure, is one of the primary causes of liver transplantation. Moreover, the diverse category of direct-acting antivirals (DAAs), which have become increasingly universal for all populations, are recommended before the disease becomes serious [1-2]. In addition, with advances in genotyping methodologies, the genotypes of HCV patients can be differentiated precisely and rapidly [3]. which is essential in the decision-making process to determine the appropriate treatment and therapeutic duration. According to the published guideline on the management of hepatitis C, different intervals of post-liver transplantation sustained virological response (SVR) monitoring are recommended for specific groups and for those who are treated with different agents [4-5]. However, recurrence after transplantation is universal even in those with undetectable HCV RNA in the early post-surgical stage [6-9]. The timing of DAA use for recurrent HCV infection after liver transplantation has been a widely discussed topic in recent years [10-14]. For patients with recurrence, several studies have suggested that DAA still exerts powerful effects in terms of SVR and its safety profile [11,13,15-17]. Guidelines for almost all patient populations have also been published [6,18]. For patients on the waiting list for transplantation, DAA agents can reduce the need for transplantation by removing the virus, but the long-term prognosis of this approach has not been confirmed [10,12] and some studies have suggested that the use of interferon-free agents before surgery will help dramatically reduce the recurrence rate after surgery [4,7,11,15]. With the exception of the safety and effectiveness of treatment before liver transplantation, similar results were also confirmed in several studies including the period of peri-operation and post-operation recurrence [16,19]. Although some research has indicated that DAAs will increase the incidence of HCC for some groups [20-22]. Research conducted in Brazil has refuted this and found no recurrence of HCC or decompensated cirrhosis after 20 months of follow-up after DAA treatment [13]. Moreover, an international multicenter study did not find that DAA therapy was a risk factor for mortality or HCC recurrence [23]. The timing of DAA treatment after liver transplantation remains a controversial issue, and no related studies have evaluated the prognosis until now. Although DAAs are beneficial for most patients, there is no effective, rapid, and non-invasive way for the clinicians to assess the prognosis of liver fibrosis and other related prognosis for patients who use DAA.

We therefore report our experience that the interval between liver transplantation and DAA agent treatment is correlated with liver fibrosis in patients with recurrent hepatitis C infection.

3. Materials and Methods

This was a retrospective observational study of liver transplant recipients with recurrent HCV infection that was performed at a single medical center in Taiwan from September 2002 to September 2019. Due to its effectiveness, non-invasive nature,24 and its ability to stratify HCC risk in patients with HCV who achieve SVR,25-26 this study adopted the Fibrosis-4 (FIB-4) score to predict the severity of hepatic fibrosis.

The formula used for FIB-4 is: age (years) AST/[platelet count (109/L) ALT1/2]. HCV RNA and genotypes were detected by the Abbott RealTime Genotype II assay, HCV RNA viral load was detected by the Roche cobas AmpliPrep/cobas TaqMan HCV Test, and HBV viral load was detected by the Abbott RealTime HBV Test.

4. Patients and Regimen

The main inclusion criteria were as follows: (1) patients at least 18 years of age who underwent a deceased-donor orthotopic liver transplantation or living donor transplantation due to complications of chronic hepatitis C infection (end-stage liver cirrhosis or hepatocellular carcinoma) (2) patients with positive HCV viral load who started DAA treatment from January 22, 2015 to September 04, 2019 (3) patients with no contraindications for DAA and no drug-drug interactions during treatment. The main exclusion criteria were as follows: (1) presence of decompensated liver disease (Child Pugh B or C) when DAA treatment was initiated (2) evidence of HCC when DAA treatment was started (3) coinfection with human immunodeficiency virus. (4) Use of DAA treatment before liver transplantation. (5) donor positive for HCV. From 2002 to 2019, 130 patients underwent liver transplantation due to liver decompensation or HCC secondary to chronic HCV infection. We detected both HCV immunoglobulin G and HCV viral load every 3 months during the first year after liver transplantation, and then monitored liver function and performed abdominal sonography every 3 months to determine whether the recurrence of HCV should be further evaluated. Among those patients, 16 were lost to follow-up after surgery and 49 died due to surgical complications, graft rejection, hepatic decompensation due to HCV recurrence or other etiology, or some extrahepatic comorbidity. HCV viral load was not detected in 33 patients, 2 had HCV recurrence without completion of DAA treatment due to impaired renal function or drug-drug interaction, 7 received DAA therapy before transplantation and were HCV-negative after surgery, and 23 received DAA after transplantation. Of these 23, 2 patients, who were considered outliers, were excluded because the interval was too long (97 months and 198 months for each patient).

The regimen comprised Ledipasvir/Sofosbuvir with or without Ribavirin, Daclatasvir/Asunaprevir/Ribavirin, Glecaprevir/Pibrentasvir, Velpatasvir/Sofosbuvir, or Sofosbuvir with or without Ribavirin. The antiviral regimen and treatment duration were decided by the treating physician based on published guidelines6,18 and treatment availability. Patients returned to the outpatient department every 4 weeks for 12 total weeks during treatment for drug refills, laboratory analyses, and evaluation of clinical side

effects and then returned every 12 weeks after treatment for laboratory analyses, sonography (performed every 12 weeks), and computed tomography (CT) (performed every 24 weeks).

5. Statistical Analyses

The baseline continuous variables of the patients are presented as the mean and standard deviation. Variables in different time points were compared using the generalized estimating equation. The correlation between the period after liver transplantation and the FIB-4 score was determined using Spearman's correlation coefficient.

Serum HCV RNA is expressed as the logarithmic transformation of the original values.

6. Ethical Considerations

This study was approved by the NDMC Ethics Committee (approval number is B202005128). In this study, we followed the Helsinki and Istanbul guidelines and no executed prisoners were used as donors.

7. Results

7.1. Baseline Patient Data

Twenty-one patients were enrolled in the present study (Tables 1, 2, 3. Table 3 in interval order). The mean age of the patients was 58.95 years, and 57.14 % (n=10) of the patients were male. The HCV RNA viral load was 6.76 log IU/mL before DAA treatment. The patients were infected with the 1a,1b, 2, 3, and 4 HCV genotypes. The reasons for liver transplantation were HCC (n=6), hepatic decompensation (n=8), and both HCC and decompensation (n=7). Seventeen patients underwent living donor liver transplantation, while the other 4 underwent deceased-donor liver transplantation. Two patients received interferon therapy before liver transplantation, but none received this therapy after surgery. Liver cirrhosis or HCC was not detected in any patient before DAA treatment. The major comorbidities were diabetes (n=9), hypertension(n=4), chronic renal disease (n=2), and coronary artery disease (n=2). The mean FIB-4 score before DAA treatment was 4.08. The mean interval between liver transplantation and DAA treatment was 19.14 months. HCV RNA was undetectable at treatment week 12 in all patients. HCV RNA was detectable (6,039,768 IU/mL) in only one patient 12 weeks after treatment, but in this case, the HCV RNA was undetectable 24 weeks after treatment. One patient treated with Ledipasvir/Sofosbuvir with Ribavirin experienced severe anemia, which subsided after Ribavirin was discontinued. Among the 4 patients who were HBV carriers before liver transplantation, no HBV DNA viral load was detected before DAA treatment; they also maintained the use of oral entecavir at a dose of 0.5 mg to prevent HBV flare-ups after liver transplantation. Then, 24 weeks after therapy cessation, sonography and CT showed no HCC or cirrhosis in any of the patients.

Table 1. The basic characteristics of the patients before operation and before the DAA usage.

Variable	**(n)**	**(%)**	**(mean)**	**(SD)**
Gender				
Female	9	42.86%		
Male	12	57.14%		
Age when operation (years)	21		56.38	7.24
Age when DAA (years)	21		58.95	7.86
The period of time of DAA after LT (months)	21		19.14	18.97

Table 2. Treatment response and FIB-4 score.

Variable	*β*	*SE*	*P value*	*95% C.I.*	
				Lower	*Upper*
Visit					
12 weeks vs. Pre-DAA	-0.490	0.995	0.622	-2.439	1.459
12 weeks after DAA vs. Pre-DAA	-1.268	0.594	0.033	-2.432	-0.103
24 weeks after DAA vs. Pre-DAA	-1.820	0.804	0.023	-3.395	-0.246
Dependent variable: FIB-4					

Table 3. The correlation between the interval and FIB-4 score.

FIB-4 score	The period of time of DAA after the liver transplantation(months)	
	Spearman's correlation coefficient	p value
pre-DAA	0.222	0.334
12 weeks	0.311	0.170
12 weeks after DAA	0.300	0.187
24 weeks after DAA	0.442	0.045

7.2. Treatment Response and FIB-4 Score

Figure 1 illustrates that in this study, the FIB-4 scores 24 weeks after DAA treatment were lower than the pre-treatment baseline scores except for the score in patient number 10 (Figure 1). According to the overall analysis using the generalized estimating equation, the mean FIB-4 of SVR12 was lower than that before DAA treatment (β=−1.268), and this difference was statistically significant (P=0.033). The mean FIB-4 score of SVR24 was lower than the pre-DAA score (β=−1.820), and this difference was statistically significant (P=0.023) (Figure 2) .

7.3. The Correlation between the Interval and FIB-4 Score

The Spearman's correlation coefficient was 0.222 for pre-DAA, 0.311 at 12 weeks after DAA treatment, 0.300 at 12 weeks after treatment, and 0.442 at 24 weeks after treatment. A positive correlation was observed in all phases. The P-value for 24 weeks post-DAA treatment was 0.045, which was statistically significant (Figure 3,). Longer intervals were correlated with high FIB-4 scores, and the correlation coefficient became higher with longer observation times.

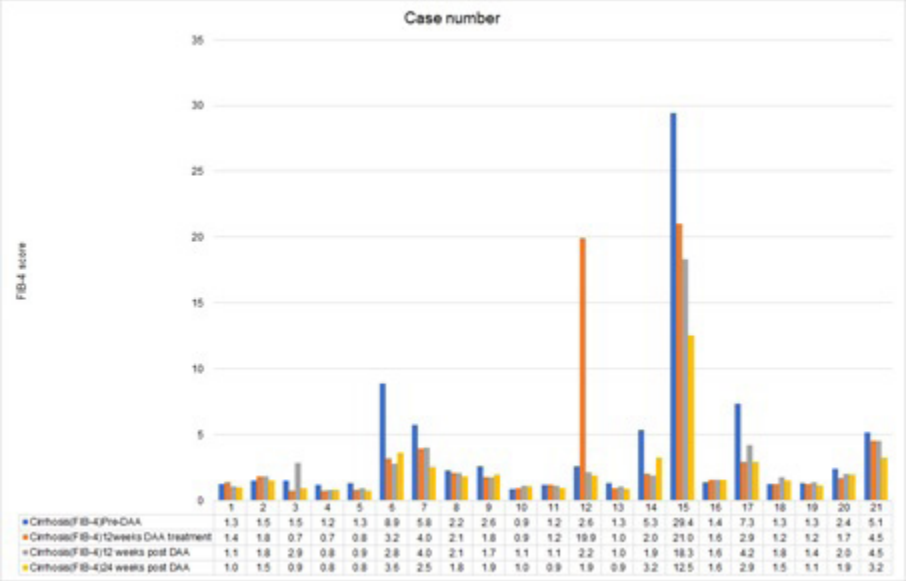

Figure 1: Illustrates that in this study, the FIB-4 scores 24 weeks after DAA treatment were lower than the pre-treatment baseline scores except for the score in patient number 10.

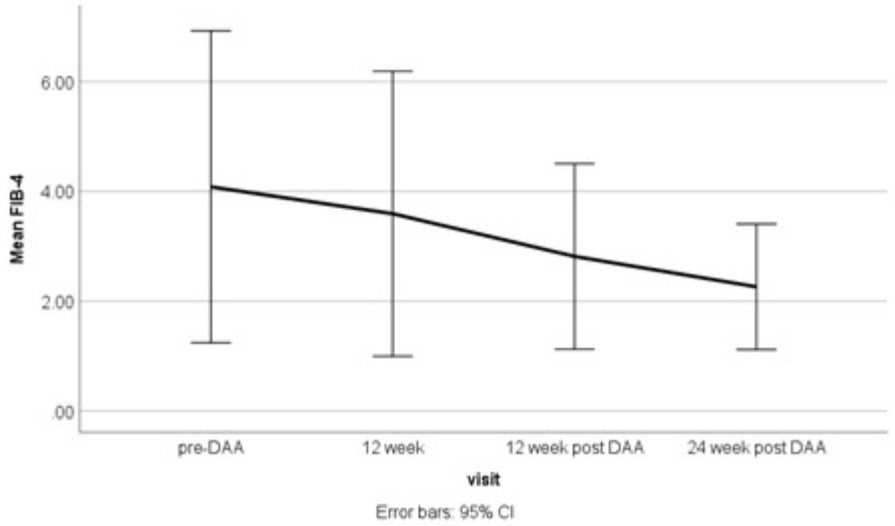

Figure 2: The mean FIB-4 score of SVR24 was lower than the pre-DAA score (β=−1.820), and this difference was statistically significant (P=0.023).

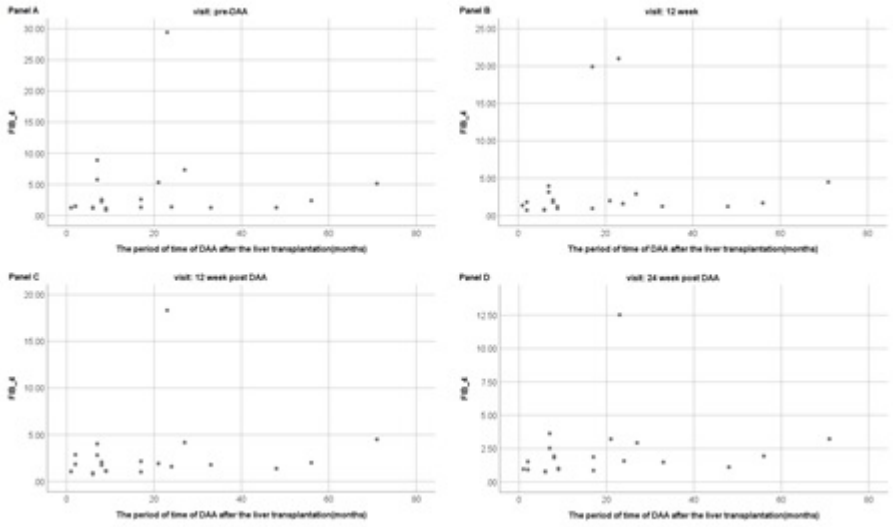

Figure 3: The P-value for 24 weeks post-DAA treatment was 0.045, which was statistically significant.

8. Discussion

As far as we know, this is the first report to evaluate the correlation between the time to DAA treatment after liver transplantation and hepatic fibrosis using the FIB-4 scoring system in a single medical center patient sample. The positive correlation provided us with information about how inferior outcomes, as measured by the fibrosis score, are associated with longer intervals, and led to a new method that can predict the prognosis of patients undergoing treatment. One of the possible reasons for this positive correlation may be the prolonged interval between HCV infection and HCV RNA detection even under regular monitoring with prompt DAA treatment. Another reason may be the post-transplantation immunosuppression that occurs in cases in which the virus is not eradicated in recipients before liver transplantation [8,14,27]. However, the decrease in FIB-4 score may be due to transaminase normalization or the increase in the number of platelets, which cannot fully reflect a change in fibrosis. With significantly improved FIB-4 score in almost all patients, patients who take the drug earlier after liver transplantation will have relatively better FIB-4 score results. Moreover, we believe that in the long-term prognosis for the liver graft after liver transplantation, the possibility of progression to fibrosis will also be relatively low for patients who take the drug earlier.

8.1. Current DAA use for Liver Transplantation with Recurrence in Taiwan

Prior to the introduction and approval of interferon-free agents, liver transplantation in HCV-positive patients was associated with poor outcomes and an increased mortality rate compared with liver transplantation for other indications [22,28]. The inferior graft and survival rates are largely due to accelerated graft fibrosis as a result of recurrent HCV infection. If left untreated, the condition will progress to cirrhosis in approximately 30% of patients at 5 years post-liver transplantation [9,14,29-31]. In Taiwan, it is mandatory for all citizens to have National Health Insurance (NHI), which has a coverage rate of approximately 99%. DAA treatment has been reimbursed by the NHI since 2017 and has been available for patients with HCV viremia regardless of their liver fibrosis status and early virologic response since 2019 [4,32-33]. The adminis-

tration of DAA before surgery not only eradicates the hepatitis C virus with a high SVR rate, but it also reduces the recurrence rate after surgery [6,11,15]. However, this treatment cannot resolve the problems of HCC and cirrhosis or serve as a substitute for the critical role of transplantation in those patients. After DAA use, some liver transplantation candidates with a lower MELD score (MELD <16) showed a remarkable clinical improvement and could be removed from the waiting list, but some with a higher MELD score may lose priority on the waiting list and experience the "MELD purgatory" effect [6,34-35].

8.2. The Variable Timing of Recurrence after Liver Transplantation

The other new perspective put forward by this study was the great variability in the timing of recurrence. In our study, HCV RNA could not be detected after surgery but was detected after an interval of post-operative follow-up that ranged from 1 month to 71 months. The latest strategies were supposed to prevent HCV recurrence,8-9,14 but it is impossible to predict precisely when recurrence occurred after surgery. Initiation of DAA treatment very early after surgery when HCV RNA is not detected seems to be an attractive treatment approach, but there are no large datasets to demonstrate its effectiveness and safety. Potential damage to liver and kidney functions after surgery and increased drug interactions with immunosuppressants have prevented the mainstream use of DAAs.6

8.3. Our Perspective on HCV Monitoring after Liver Transplantation

An early study reported that the HCV viral load only reflects the amount of virus present in the liver but that the viral load was not correlated with aminotransferase levels or the histological diagnosis,36 and recurrence could not be evaluated by liver function test. No definite guidelines exist for the interval of HCV monitoring, and thus, the interval can only be evaluated by clinicians. Since the interval between liver transplantation and DAA treatment has become a new way to predict prognosis in our study and due to the unexpected timing of HCV RNA detection, regular HCV viral load monitoring was needed for all patients. Our experience suggested that due to the high possibility of recurrence within 2 years (76.1%), the HCV viral load should be monitored immediately after surgery and then at 12-week intervals for at least 2 years, even when liver function tests are within the normal range. More than 10% of recipients (16/130) were observed without regular follow-up at 1 medical center even under the system of Taiwan's NHI with over 99% coverage for all Taiwanese nationals.32-33 For the reasons mentioned above, we supposed that many liver recipients in regions where HCV is prevalent do not undergo regular follow-up after liver transplantation under different medical systems, and some may have even abandoned treatment after intolerance to interferon therapy or other agents during the early period.

9. Limitations

Limitations of this study include its observational nature and small sample size. HCV carriers who undergo liver transplantation, experience HCV recurrence, and who are treated with DAA have comprised relatively small groups in the past. In the future, more cross-participation among medical centers and even cross-border cooperation are needed to include more samples and a higher reference value. Moreover, although transient elastography or liver biopsy will provide more information, the characteristics and advantages of this test that it is non-invasive and the results can be quickly determined.

10. Conclusion and Practical Application

DAA use before transplantation is the best time for most recipients according to the latest published guideline. For the patients who were not administered DAA before liver transplantation, the appropriate timing of DAA use for HCV infection after liver transplantation is soon after the HCV viral load is detected due to the higher possibility of developing liver cirrhosis with the period of time after liver transplantation. This is especially true in patients who were negative for HCV in the early disease phase and who were then lost to regular follow-up and those who had received interferon, which failed due to intolerance. The potential population of patients with HCV recurrence might be underestimated, and the overall prognosis of patients with hepatic fibrosis who are prepared to use DAA might be correlated with the interval between liver transplantation and the initiation of DAA treatment.

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