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***Observational Study***

**Efficacy and safety of combined directly acting antivirals for the treatment of Chinese chronic hepatitis c patients in a real-world setting**

Chen JH *et al*. Efficacy and safety of DAAs in Chinese CHC patients

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**Abstract**

***AIM***

to explore the efficacy and safety of combined directly acting antivirals (DAAs) for the treatment of Chinese chronic hepatitis C (CHC) patients in a Real-World setting.

***METHODS***

CHC patients who were treated with DAAs while hospitalized in Peking University First Hospital between January 2015 and December 2016 were enrolled. Samples and clinical data were collected at 0 wk, 2 wk, 4 wk, 8 wk, 12 wk, or 24 wk during DAAs treatment and at 4 wk, 12 wk, and 24 wk after the end of treatment.

***RESULTS***

Fifty-four patients who underwent DAAs treatment were included in our study. 83.3% (45/54) patients achieved rapid virological response at 2w after treatment initiation (RVR 2); 94.4% (51/54) patients achieved sustained virological response at 24 wk after the end of treatment (SVR 24). Serum creatinine and uric acid levels at the end of treatment were significantly increased than baseline levels (83.6 ± 17.9 *vs* 88.8±19.4, *P*01 < 0.001; 320.8 ± 76.3 *vs* 354.5 ± 87.6, *P*01 < 0.001), and no significant improvements were observed at 24w after the end of treatment (83.6 ± 17.9 *vs* 86.8 ± 19.1, *P*02 = 0.039; 320.8 ± 76.3 *vs* 345.9 ± 89.4, *P*02 = 0.001). The total frequency of adverse events (AEs) during treatment was 33.3% (18/54), the major AEs were fatigue (16.7%), headache (7.4%), anorexia (7.4%), and insomnia (5.6%).

***CONCLUSION***

Though based in a small cohort of patients, the abnormal changes in renal function indices and relative high frequency of AEs during combined DAAs treatment should be taken as a note of caution.

**Key words:** Chronic hepatitis C; Directly acting antivirals; Efficacy; Safety; China

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**Core tip:** Treatment of hepatitis C virus (HCV) infection has reached a new era with the approval of directly acting antivirals (DAAs), while there had been limited data on the use of DAAs treatment in a real-world setting in China. We explored the changes of hepatorenal function indices before and after DAAs treatment and found that serum creatinine and uric acid levels at the end of treatment were significantly increased than baseline levels, and no significant improvements were observed at 24 wk after the end of treatment. This study may serve as a reminder to clinicians to implement close renal function monitoring in patients receiving combined DAAs treatment.

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**INTRODUCTION**

Chronic hepatitis C virus (HCV) infections affect approximate 130-150 million people worldwide, as a major cause of liver cirrhosis and hepatocellular carcinoma[1-3]. Treatment of HCV infection has reached a new era with the approval of first generation directly acting antivirals (DAAs) in 2011 and the subsequent development of interferon (IFN)-free, all-oral DAAs combination regimens[4]. All-oral DAAs combination regimens simplified the treatment and improved compliance of patients who disliked injections or were intolerable to them[5]; combined DAAs regimens shortened treatment durations from 48 wk to 12 wk or 24 wk period, Sofosbuvir (SOF)/Velpatasvir also attained a promising efficacy at 8 wk, and some studies tried to shorten treatment times even further[6]; similar to cocktail therapies against human immunodeficiency virus, combination therapies that target different stages of the HCV life cycle have been conceived to avoid cross-resistance[7]; importantly, all-oral combination regimens increased sustained virological response (SVR) rates to more than 90% with fewer contraindications and adverse events (AEs) in patients with different HCV genotype (GT) infection, liver conditions, treatment experiences and concomitant diseases[8-14]; Sofosbuvir (SOF)/Velpatasvir combination regimen might even provide complete pan-genotypic treatment for patients with HCV infection[15,16]. Though price decreases for HCV drugs have already been announced for some DAAs, most of them are currently too expensive for governments worldwide to deliver on their promise to cure and eliminate the disease, especially in low- and middle-income countries[17].

China has the greatest number of chronic hepatitis C (CHC) cases worldwide, with an estimated 29.8 million patients infected, GT 1b and GT 2a are the two major HCV subtypes, accounting for 62.78% (95%CI: 59.54%–66.02%) and 17.39% (95%CI: 15.67%–19.11%), respectively[18,19]. The traditional treatment for patients with CHC in China is peginterferon in combination with ribavirin (PegIFNα-2a/RBV, PR), which was found to be associated with lower SVR rates and more AEs[20]. Refractory CHC patients and patients with contraindications and intolerances to the AEs associated with PR treatment try to initiate DAAs treatment.

So far, there had been limited data on the use of combined DAAs treatment in a real-world setting in China. This study aimed to show the efficacy of DAAs for the treatment of Chinese CHC patients and explore the effects of DAAs on hemogram and hepatorenal function indices, and the frequency of AEs during treatment in a real-world setting.

**MATERIALS AND METHODS**

***Patients***

CHC patients who were treated with DAAs while hospitalized in Peking University First Hospital between January 2015 and December 2016 and met the following criteria were enrolled in this study: (1) infected with HCV GT 1b or 2a; (2) negative for hepatitis A virus immunoglobulin (Ig) M, hepatitis B surface antigen, hepatitis E virus Ig M and human immunodeficiency virus; (3) no severe heart disease; (4) no active drug users; (5) no severe renal function damage or renal failure (eGFR < 30 ml/min); (6) no pregnancy; (7) appropriate DAAs treatment regimens; and (8) clinical information is intact. Total of 16 patients were excluded including one HBV/HCV co-infected patient, 3 patients with severe renal function damage, one patients treated with inappropriate DAAs regimens, and 11 patients with incomplete clinical information. All study participants provided informed written consent prior to study enrollment. Ethical approval was given by the Ethics Committee.

***Clinical data collection and assessment***

Hematological, biochemical, and urine tests were performed at 0 wk, 2 wk, 4 wk, 8 wk, 12 wk, or 24 wk during DAAs treatment, as well as 4 wk, 12 wk, and 24 wk after the end of treatment at clinical laboratory[21]. White blood cell (WBC) count, red blood cell (RBC) count, hemoglobin concentration (HGB), and blood platelet (PLT) count were used to assess the changes of hemogram; alanine aminotransferase (ALT), aspartate aminotransferase (AST), FIB-4 score, and liver stiffness measurement (LSM) were used to assess degree of liver inflammation and fibrosis; estimated glomerular filtration rate (eGFR), serum creatinine (Scr), uric acid (UA), and blood urea nitrogen (BUN) were used to assess renal function.

LSM were measured by transient elastography (Fibroscan, Echosens, Paris). Presence of cirrhosis was determined by LSM > 17.5 kPa[22-24]. FIB-4 score was calculated with equation: FIB-4 = [AGE \* AST (U/L)] / [PLT (109/L) \* ALT (U/L) ^ (1/2)][25]. The eGFR was calculated with the Modification of Diet in Renal Disease Study equation adjusted for Chinese population: eGFR = 175 \* (serum creatinine)-1.234 \* age-0.179 \* 0.79 (if female)[26].

HCV RNA quantitation and genotyping were measured at the virus laboratory in department of infectious disease. Serum HCV RNA quantitation was measured using a COBAS Taqman HCV Test kit (Roche Molecular Systems Inc., Pleasanton, CA, United States); COBAS AmpliPrep instrument was used for automated specimen processing and COBAS Taqman analyser was used for automated amplification and detection[27]; the detailed detection procedures were performed according to the manufacturer’s instructions. HCV genotypes were determined by restriction fragment length polymorphism (RFLP) analysis of the amplified 5′-noncoding genome region[28], detailed procedures were performed according to the protocol described below: HCV RNA was extracted from 140 μL serum samples using QIAamp viral RNA mini kit (Qiagen, Hilden, Germany); reverse transcription and Polymerase chain reaction (PCR) amplification, using BG1 (5’-CTGTGAGGAACTACTGTCTT-3’) and BG2 (5’-AACACTACTCGGCTAG CAGT-3’) as upstream and downstream primers for the first round reaction (reaction system: 2 × Buffer 15 µL +BG1 1 µL + BG2 1 µL + cDNA 10 µL + H2O 3 µL ; conditions: Denaturing 95 ℃ × 2 min, 30 rounds × annealing 94 ℃ × 30 s + 55 ℃ × 30 s + 72 ℃ × 60 s, and extending 72 ℃ × 7 min) and BG3 (5’-TTCACGCAGAAAGCGTCTAG-3’) and BG4 (5’-GTTGATCCA AGAAAGGACCC-3’) as upstream and downstream primers for the second round reaction (reaction system: 2 × Buffer 15 µL +BG1 1 µL + BG2 1 µL + cDNA 10 µL + H2O 3 µL ; conditions: Denaturing 95 ℃ × 2 min, 30 rounds × annealing 94 ℃× 30 s + 60 ℃× 30 s + 72 ℃× 60 s, and extending 72 ℃× 7 min); the PCR productions were purified using QIAquick PCR Purification Kit (Qiagen, Hilden, Germany) and digested with Hae III at 37℃ for 2 hours (reaction system: 10 × Buffer 2 µL + Hae III 2.3 µL + ddH2O 9.7 µL + PCR production 6 µL) and agarose gel electrophoresis was performed to analyse the RFLP of the digestion products.

***Statistical analysis***

Microsoft Excel (Microsoft, Redmond, Washington, United States) was used for data collection and analysis. Data were expressed as mean ± sd or count number. We used Student’s *t*-test, the Fisher’s exact test or **2 test to calculate the statistical difference of baseline characteristics between different HCV GT infected patients. Repeated measures of the general linear model in SPSS were used to make repeated measures analysis of variance to give comparison among different groups, different time points and calculate the interaction effect between treating factors and time factors. Mauchly’s test of spherecity was used to judge whether there were relations among the repeatedly measured data. If any *P* < 0.05, Greenhouse- Geisser corrected results should be taken; Bonferroni or Fisher’s Least Significant Difference tests (when Epsilon < 0.7, Bonferroni test) were used to do pairwise comparisons of the repeatedly measured data in different measurement time. We carried out statistical analysis with SPSS version 16.0. *P* < 0.05 was considered statistically significant.

**RESULTS**

***Baseline characteristics of enrolled patients***

Total of 54 patients underwent DAAs treatment were enrolled in our study, including 40 HCV GT 1b infected patients and 14 HCV GT 2a infected patients; the mean age was 55.4 ± 16.6 years, 29 were male, 21 were PR treatment experienced, and 20 had cirrhosis; the mean scores of LSM were 15.9 ± 14.1 (kPa), and the mean PLT count was 147.1 ± 65.1 (109/L). Baseline characteristics for all 54 CHC patients are shown in Table 1. The distribution of PR treatment experienced patients and cirrhotic patients and all other baseline characteristics did not differ significantly between HCV GT 1b infected patients and HCV GT 2a infected patients (Table 1).

***Treatment efficacy***

Among the 40 HCV GT1b infected patients, 15 were treated with SOF + Daclatasvir (DAC) and 25 were treated with SOF/Ledipasvir (LDV); among the 14 HCV GT2a infected patients, 6 were treated with SOF + DAC and 8 were treated with SOF + Ribavirin (RBV) (< 75 kg, 1000 mg/d; >75 kg, 1200 mg/d). All non-cirrhotic patients were treated for 12 wk, HCV GT 1b infected patients with cirrhosis were treated for 24 wk, HCV GT 2a infected patients with cirrhosis were treated with SOF + DAC for 12 wk or SOF + RBV for 20 wk[29].

83.3% (45/54) patients achieved rapid virological response at 2w after treatment initiation (RVR 2), while 9 patients including four HCV GT1b infected patients treated with SOF + DAC, three HCV GT1b infected patients treated with SOF/LDV, one HCV GT2a infected patient treated with SOF + DAC, and one HCV GT2a infected patient treated SOF + RBV had detectable HCV RNA. Of these 9 patients, 4 were PR treatment experienced, 5 were treatment naïve; 4 were cirrhotic, 5 were non-cirrhotic. At the end of treatment, 96.3% (52/54) patients achieved virological response, while one HCV GT1b infected patient treated with SOF/LDV for 12 wk and one HCV GT2a infected patient treated with SOF + DAC for 12 wk still had detectable HCV RNA; SVR rates at 24 wk after the end of treatment (SVR 24) were 94.4% (51/54), and one GT2a patient treated with SOF + RBV for 20 wk relapsed at 12 wk after the end of treatment (Figure 1).

When patients were classified by HCV GT, PR treatment experience, DAAs regimens and liver condition, RVR 2 rates were 73.3% (11/15) in HCV GT 1b infected patients treated with SOF + DAC, 88.0% (22/25) in HCV GT 1b infected patients treated with SOF/LDV, 83.3% (5/6) in HCV GT 2a infected patients treated with SOF + DAC, 87.5% (7/8) in HCV GT 1b infected patients treated with SOF + RBV, 84.8% (28/33) in PR treatment naive patients, 81.0% (17/21) in PR treatment experienced patients, 85.3% (29/34) in non-cirrhotic patients, and 80.0% (16/20) in cirrhotic patients; SVR 24 rates were 97.5% (39/40) in HCV GT 1b infected patients, 85.7% (12/14) in HCV GT 2a infected patients, 93.9% (31/33) in PR treatment naive patients, 95.2% (20/21) in PR treatment experienced patients, 94.1% (32/34) in non-cirrhotic patients, and 95.0% (19/20) in cirrhotic patients.

***Changes of clinical indices before and after combined DAAs treatment***

The changes of clinical indices among different observing points at the end of treatment and at 24w after the end of treatment compared with baseline data in 54 included patients are shown in Table 2. For all patients, ALT and AST levels at the end of treatment and at 24 wk after the end of treatment were significantly decreased than baseline levels (ALT: 54.6 ± 36.3 *vs* 20.3 ± 13.3, *P*01 < 0.001; 54.6 ± 36.3 *vs* 17.1 ± 6.9, *P*02 < 0.001. AST: 50.8 ± 33.1 *vs* 24.4 ± 10.4, *P*01 < 0.001; 50.8 ± 33.1 *vs* 22.4 ± 7.0, *P*02 < 0.001). Post-treatment FIB-4 score exhibited a continued reduction (4.07 ± 4.35 *vs* 2.94 ± 2.76, *P*01 < 0.001; 2.94 ± 2.76 *vs* 2.61 ± 2.21, *P*12 = 0.003) compared with that at baseline (Table 2). At the end of treatment, eGFR level had a significant decrease (eGFR: 87.1 ± 19.5 *vs* 81.2 ± 20.0, *P*01 = 0.001), serum creatinine (Scr) and uric acid (UA) levels were significantly increased than baseline levels (Scr: 83.6 ± 17.9 *vs* 88.8 ± 19.4, *P*01 < 0.001; UA: 320.8 ± 76.3 *vs* 354.5 ± 87.6, *P*01 < 0.001) and no significant improvements were observed at 24 wk after the end of treatment (Scr: 83.6 ± 17.9 *vs* 86.8 ± 19.1, *P*02 = 0.039; UA: 320.8 ± 76.3 *vs* 345.9 ± 89.4, *P*02 = 0.001). Blood urea nitrogen (BUN) level at the end of treatment had no significant changes compared with baseline level, while an increased BUN level was observed at 24w after the end of treatment (5.17 ± 1.50 *vs* 5.65 ± 1.80, *P*02 = 0.009) (Figure 2). DAAs regimens and time points had no interactive effects on the changes of hepatorenal function indices, the interactive effects on changes of RBC and HGB may be caused by RBV (Table 2). Combined DAAs treatment had no significant effect on the WBC count, RBC count and HGB concentration; however, the PLT count had a remarkable increase at 24w after the end of treatment compared with that at baseline (147.1 ± 65.1 *vs* 158.2 ± 65.9, *P*02 = 0.008) (Table 2).

***AEs during combined DAAs treatment***

The frequency of AEs during treatment was 33.3% (18/54), the major AEs were fatigue (16.7%), headache (7.4%), anorexia (7.4%), and insomnia (5.6%), and most of them were mild and tolerable. One GT1b patients treated with SOF+DAC discontinued the treatment at 8w due to the development of renal area pain (Table 3). The common AEs during traditional PR treatment, like fever, anemia, neutropenia, and thrombocytopenia rarely occurred during DAAs treatment, only two patients treated with SOF+RBV were observed with mild anemia.

**DISCUSSION**

The availability and development of DAAs revolutionized the management of HCV infection. In America, Europe, Japan, and many other countries, DAAs achieved high SVR rates with low frequency of AEs in clinical trials and real-world cohorts[7], while limited data was available in china. Considering the ethnic, regional, and virological difference, we analyzed the efficacy and safety of combined DAAs for treatment of 54 Chinese CHC patients in a real-world setting.

This study showed a promising SVR rate as in other countries and areas, while abnormal changes in renal function indices and relative more AEs were unexpected. In this study, 83.3% (45/54) patients achieved RVR 2 and 94.4% (51/54) patients achieved SVR 24 which had no significant differences with that reported in previous studies[30-33]. With the application of DAAs, some cases were reported with nephrotoxicity and hepatotoxicity due to DAAs treatment[34,35]. Thus, our study analyzed the changes of hemogram and hepatorenal function indices and the frequency of AEs associated with combined DAAs treatment. After the treatment, liver function indices and FIB-4 score reflecting the liver fibrosis stage had significant improvements. Different with traditional PR treatment, DAAs had no significant effect on hemogram, and along with the improvement of liver function, PLT count at 24 wk after the end of treatment were significantly increased compared with baseline. However, the mean Scr and UA levels at the end of treatment had a significant elevation compared with those at baseline, and there was no trend toward improvement at 24 wk after the end of treatment. The specific reasons for changes of renal function indices was unknown, considering no abnormal changes in renal function indices were found in clinical trials[29,36,37], the potential drug-drug interactions between combined DAAs regimens and complicated concomitant medications in this real-world cohorts may be the major reason. Our study showed relatively more AEs associated with the use of combined DAAs treatment, the major AEs were fatigue, headache, anorexia, and insomnia. Though most of them were mild and tolerable, more attention should be paid during the treatment.

Though based on a small cohort of patients, the abnormal changes in renal function indices and relative more AEs during treatment should be taken as a note of caution. Clinical physicians should implement close renal function monitoring and attach importance to AEs occurring in patients receiving combined DAAs treatment.

**comments**

***Background***

Treatment of hepatitis C virus (HCV) infection has reached a new era with the approval of directly acting antivirals (DAAs). All-oral DAAs combination regimens have achieved high sustained virological response (SVR) rates with minor contraindications and adverse events. China has the greatest number of chronic hepatitis C (CHC) cases worldwide, with an estimated 29.8 million patients infected, while there had been limited data on the use of combined DAAs treatment in a real-world setting in China.

***Research frontiers***

In China, there had been limited data on the use of combined DAAs treatment in a real-world setting. The research hotspot is to show the efficacy of DAAs for treatment of Chinese CHC patients and explore the effects of DAAs on hemogram and hepatorenal function indices, and the frequency of adverse events (AEs) during treatment in a real-world setting.

***Innovations and breakthroughs***

The changes of clinical indices among different observing points during combined DAAs treatment were analysed. At the end of treatment, eGFR level had a significant decrease, serum creatinine (Scr) and uric acid (UA) levels were significantly increased than baseline levels and no significant improvements were observed at 24w after the end of treatment. On the other hand, the current data also showed a high frequency of AEs during combined DAAs treatment (33.3%), the major AEs were fatigue, headache, anorexia, and insomnia.

***Applications***

The data in this study showed the abnormal changes in renal function indices and relative high frequency of AEs during combined DAAs treatment. This study would remind clinical physicians of implementing close renal function monitoring and focusing on AEs occurring in patients receiving combined DAAs treatment.

***Terminology***

DAAs are inhibitors directly acting on different viral targets, including NS3 protease inhibitors, NS5A inhibitors, nucleoside/nucleotide analogues, and non-nucleoside inhibitors of the RNA-dependent RNA polymerase. In 2011, Telaprevir and Boceprevir opened a new area for HCV therapy, while these 2 NS3/4 protease inhibitors are given in combination with pegylated interferon and ribavirin. Subsequent all-oral DAAs combination regimens have achieved high SVR rates with fewer contraindications and AEs.

***Peer-review***

The chosen topic is currently one of the hot topics and of great interest to a lot of clinicians. The last few years have witnessed significant progress in HCV therapy by replacing of IFN + ribavirin combined therapy with oral compounds acting directly to inhibit HCV replication (DAAs). DAAs target multiple steps in the HCV life cycle and are currently used in combination to treat HCV infection without need of IFN.

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**Patients treated with DAAs (*n* = 54)**

**Patients with GT1b CHC (*n* = 40)**

**Patients with GT2a CHC (*n* = 14)**

**DCV (60 mg/d)/**

**SOF (400 mg/d)**

**(*n* = 15)**

**LDV (90 mg/d)/**

**SOF (400 mg/d)**

**(*n* = 25)**

**DCV (60 mg/d)/**

**SOF (400 mg/d)**

**(*n* = 6)**

**RBV (1000or1200 mg/**

**d)/SOF (400 mg/d)**

**(*n* = 8)**

***n* = 11**

***n* = 22**

***n* = 5**

***n* = 7**

***n* = 15**

***n* = 24**

***n* = 5**

***n* = 8**

***n* = 15**

***n* = 24**

***n* = 5**

***n* = 7**

**HCV GT**

**DAAs**

**RVR 2 = 83.3%**

**End-of-treatment**

**SVR 24=94.4%**

**Figure 1 Diagram of detailed treatment regimens for 54 chronic hepatitis C patients and the treatment efficacy.** CHC: chronic hepatitis C; RVR 2: rapid virological response at 2 wk after treatment initiation; SVR 24: sustained virological response at 24 wk after the end of treatment.

***P*01< 0.001**

***P*01< 0.001**

***P*01= 0.757**

***P*02= 0.039**

***P*02= 0.001**

***P*02= 0.009**

***P*01= 0.001**

***P*02= 0.097**

**A**

**B**

**C**

**D**

**Figure 2 Changes of renal function indices among different observing points.** A: eGFR; B: Scr; C: UA; D: BUN. T0: Baseline; T1: End of treatment; T2: 24 wk after the end of treatment. eGFR: estimated glomerular filtration rate; Scr: serum creatinine; UA: uric acid; BUN: blood urea nitrogen.

**Table 1 Baseline characteristics of enrolled patients**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristics** | **All (*n =* 54)** | **GT1b (*n =* 40)** | **GT2a (*n =* 14)** | ***P*(1b *vs* 2a)** |
| Age | 55.4±16.6 | 57.2±15.9 | 50.1±18.1 | 0.175 |
| Male/Female | 29/25 | 21/19 | 8/6 | 0.764 |
| HCV RNA log10 (IU/ml) | 6.48±0.97 | 6.63±0.89 | 6.06±1.1 | 0.058 |
| PR(experienced/naive) | 21/33 | 17/23 | 4/10 | 0.358 |
| non-cirrhotic/cirrhotic | 34/20 | 24/16 | 10/4 | 0.446 |
| LSM (kPa) | 15.9±14.1 | 17.5±15.1 | 11.4±9.8 | 0.162 |
| FIB-4 score | 4.07±4.35 | 4.14±3.53 | 3.87±6.29 | 0.847 |
| ALT (IU/L) | 54.6±36.3 | 57.4±38.7 | 46.5±27.9 | 0.339 |
| AST (IU/L) | 50.8±33.1 | 50.6±26.8 | 46.3±37.1 | 0.555 |
| eGFR(ml/min per 1.73 m2) | 87.1±19.5 | 87.2±20.9 | 86.5±15.7 | 0.908 |
| Scr (μmol/L) | 83.6±17.9 | 83.3±19.5 | 84.4±12.9 | 0.848 |
| UA (μmol/L) | 320.8±76.3 | 315.2±78.5 | 337.4±72.9 | 0.349 |
| BUN (mmol/L) | 5.17±1.50 | 5.21±1.52 | 5.12±1.55 | 0.881 |
| WBC (109/L) | 4.85±1.67 | 4.67±1.65 | 5.35±1.70 | 0.192 |
| RBC (1012/L) | 4.42±0.64 | 4.40±0.67 | 4.49±0.59 | 0.652 |
| HGB (g/L) | 140.8±17.2 | 139.9±17.9 | 143.6±15.6 | 0.492 |
| PLT (109/L) | 147.1±65.1 | 143.0±68.4 | 158.8±55.0 | 0.439 |

HCV: hepatitis C virus; ALT: alanine aminotransferase; AST: aspartate aminotransferase; Scr: serum creatinine; UA: uric acid; BUN: blood urea nitrogen; LSM: Liver stiffness measurement; eGFR: Estimated glomerular filtration rate.

**Table 2 Change of clinical indices before and after combined directly acting antivirals treatment**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | T0 | T1 | T2 | *P*01 | *P*12 | *P*02 | *P*(DAAs\*Time) |
| FIB-4 score | 4.07±4.35 | 2.94±2.76 | 2.61±2.21 | 0.001 | 0.003 | < 0.001 | 0.399 |
| ALT (IU/L) | 54.6±36.3 | 20.3±13.3 | 17.1±6.9 | < 0.001 | 0.061 | < 0.001 | 0.594 |
| AST (IU/L) | 50.8±33.1 | 24.4±10.4 | 22.4±7.0 | < 0.001 | 0.006 | < 0.001 | 0.733 |
| eGFR(ml/min/1.73m2) | 87.1±19.5 | 81.2±20.0 | 83.6±21.2 | 0.001 | 0.174 | 0.097 | 0.646 |
| Scr (μmol/L) | 83.6±17.9 | 88.8±19.4 | 86.8±19.1 | < 0.001 | 0.137 | 0.039 | 0.481 |
| UA (μmol/L) | 320.8±76.3 | 354.5±87.6 | 345.9±89.4 | < 0.001 | 0.212 | 0.001 | 0.299 |
| BUN (mmol/L) | 5.17±1.50 | 5.12±1.40 | 5.65±1.80 | 0.757 | 0.003 | 0.009 | 0.858 |
| WBC (109/L) | 4.85±1.67 | 4.91±1.54 | 5.00±1.34 | 0.725 | 0.595 | 0.342 | 0.536 |
| RBC (1012/L) | 4.42±0.64 | 4.43±0.68 | 4.50±0.68 | 0.822 | 0.345 | 0.223 | 0.023 |
| HGB (g/L) | 140.8±17.2 | 139.4±20.9 | 141.1±21.1 | 0.467 | 0.443 | 0.860 | 0.026 |
| PLT (109/L) | 147.1±65.1 | 153.6±67.5 | 158.2±65.9 | 0.053 | 0.117 | 0.008 | 0.540 |

T0: Baseline; T1: end of treatment; T2: 24 wk after the end of treatment. *P*01: significance of difference between T0 and T1; *P*12: significance of difference between T1 and T2; *P*02: significance of difference between T0 and T2; *P*(DAAs\*Time): interactive effects of DAAs regimens and time points on the changes of renal function indices. ALT: alanine aminotransferase; AST: aspartate aminotransferase; Scr: serum creatinine; UA: uric acid; BUN: blood urea nitrogen; LSM: Liver stiffness measurement; eGFR: Estimated glomerular filtration rate; DAAs: directly acting antivirals.

**Table 3 Frequency of adverse events during combined directly acting antivirals treatment *n*(%)**

|  |  |  |  |
| --- | --- | --- | --- |
| **AEs** | **indices**  | **AEs** | **indices** |
| Fatigue | 9 (16.7)  | pruritus | 1 (1.9)  |
| Headache | 4 (7.4)  | anxiety | 1 (1.9)  |
| Anorexia | 4 (7.4)  | renal area pain | 1 (1.9)  |
| Insomnia | 3 (5.6)  | treatment discontinuation | 1 (1.9)  |
| Anemia | 2 (3.7)  | Total  | 18 (33.3)  |

AEs: adverse events.