**HUE UNIVERSITY**

**UNIVERSITY OF MEDICINE AND PHARMACY**

**TRAN NGUYEN AI THANH**

# CHANGES IN LIVER FIBROSIS AMONG PATIENTS WITH CHRONIC HEPATITIS C VIRUS GENOTYPE 1 OR 6 TREATED WITH THE COMBINATION THERAPY OF SOFOSBUVIR AND LEDIPASVIR

**SUMMARY OF MEDICAL DOCTORAL DISSERTATION**

**HUE, 2022**

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The thesis will be defended in front of the Thesis Evaluation Council of Hue University

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**SPECIALTY: INTERNAL MEDICINE**

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# INTRODUCTION

## 1. Background

Chronic hepatitis C (CHC) is an important global health issue. According to the World Health Organization (WHO), in 2019 there were 71 million people infected with Hepatitis C virus (HCV) worldwide and being at risk of cirrhosis and death if left untreated. In Vietnam, the HCV infection rate is quite high, about 1% - 4%. HCV cure reduces the risk of HCC (Hepatocellular carcinoma) and mortality, improves liver fibrosis in patients with CHC.

HCV is currently classified into 8 genotypes. In Vietnam, genotype 6 (52.7% - 87.6%) and 1 (6.7% - 30.4%) are the two most common genotypes in Vietnam. Genotype 6 has a high incidence of drug resistance and there are very few clinical trials evaluating the effectiveness of DAA (direct-acting antiviral) regimens conducted on patients with HCV genotype 6 infection.

In recent years, thanks to the introduction of DAAs, there have been many breakthroughs in the treatment of CHC with a very high eradication rate (> 95%) and a low frequency of side effects. The combination therapy of sofosbuvir and ledipasvir (SOF/LDV) is one of the pioneering regimens that have been proven to be effective in achieving a sustained virological response (SVR). Also, this regiment is cost-effective and can be affordable for many patients in Vietnam. The proportions of patients infected with HCV-1 or HCV-6 achieving SVR with SOF/LDV regimen was about 97-99% and 95.4% in cirrhotic patients.

Up until now, there have not been many Vietnam's publications evaluating the effectiveness of SOF/LDV regimens in patients with CHC (especially in the Child-Pugh A group), the role of non-invasive methods for evaluating liver fibrosis in predicting the ability to achieve SVR as well as in monitoring the improvement of liver fibrosis after the antiviral therapy. These problems are very important in the treatment of CHC patients infected with HCV-6, which is an uncommon genotype in the world. Therefore, we conduct the study "Changes in liver fibrosis among patients with chronic hepatitis c virus genotype 1 or 6 treated with the combination therapy of sofosbuvir and ledipasvir" with the following objectives:

*1. To evaluate clinical, biochemical and virological responses among patients with chronic hepatitis C virus genotypes 1 or 6 treated with a 12-week regimen of sofosbuvir/ledipasvir.*

*2. To assess the improvement of liver fibrosis by measuring transient liver elastography and FIB-4 at the following time points: the end of treatment, 12 weeks and 24 weeks after the end of treatment with the above regimen and related factor.*

**2. The urgency of the study**

Currently, monitoring the improvement of liver fibrosis is becoming more important than achieving SVR. Effective antiviral therapy will result in the improvement of liver fibrosis.

Liver biopsy is increasingly replaced by non-invasive methods for evaluating liver fibrosis in most cases. Liver elastography, especially Fibroscan has been approved by FDA for its effectiveness and reliability in the measurement of liver fibrosis. The degree of improvement in liver fibrosis was significantly higher in patients treated with DAA therapy than in patients treated with interferon (IFN). In patients with severe fibrosis, the measurements of liver fibrosis should be performed for long-term follow-up after SVR achievement because the fibrosis persists after SVR has been achieved.

**3. Scientific significance**

- Research results contribute more evidence on the effectiveness and safety of SOF/LDV regimen in clinical, biochemical, virological and liver fibrosis improvement. Given the very high eradication rate of this regimen, the degree of liver fibrosis after eradication plays an important role in the follow-up after treatment discontinuation. The significant improvement of liver fibrosis measured by Fibroscan at 24 weeks after the end of treatment reinforces the recommendation that Fibroscan should be measured every 24 weeks after treatment in patients with significant cirrhosis.

- Research results also demonstrate the role of Fibroscan and Fib-4 in monitoring the improvement of liver fibrosis in the treatment of CHC. In addition, identifying the factors that affect the improvement of liver fibrosis after antiviral therapy in patients with CHC also helps in planning necessary interventions.

**4. Practical significance**

- The study results suggest DAA regimens, specifically SOF/LDV should be prioritized because of its effectiveness and safety.

- It is recommended that the assessment of liver fibrosis should be performed before and after SOF/LDV regimen by measuring liver elastography and FIB-4, helping to plan supportive treatment for patients with factors predicting slow fibrosis improvement to optimize the treatment effectiveness.

**5. Thesis layout**

The thesis has 121 pages including: introduction with 2 study objectives (2 pages), literature review (38 pages), materials and methods (17 pages), results (32 pages), discussion (27 pages). The conclusion is 2 pages and includes 4 recommendations.

The thesis contains 45 tables, 14 charts, 1 diagrams and 11 pictures.

The annex has 243 references, including 29 Vietnamese documents and 214 English documents.

# Chapter 1
# LITERATURE OVERVIEW

## 1.1. EPIDEMIOLOGICAL, VIRAL CHARACTERISTICS AND DIAGNOSTIC OF CHRONIC HEPATITIS C VIRUS

### 1.1.1. Epidemiology

According to WHO 2019, there are about 71 million people are infected with HCV worldwide, accounting for approximately 1% of the population. In Vietnam, the prevalence of HCV infection is about 1-4%, mainly genotypes 1 and 6.

### 1.1.2. Natural history

Liver damage in CHC varies from minimal necrotizing inflammation to extensive fibrosis, cirrhosis. Factors that influence the progression of CHC including age, duration of infection, degree of inflammation and fibrosis, hepatic iron deposition, alcohol abuse, HBV and HIV co-infections, nonalcoholic steatohepatitis and obesity. CHC is the second leading cause of HCC (after HBV).

### 1.1.3. The molecular biology and life cycle of HCV

*1.1.3.1. HCV molecular biology*

*1.1.3.2. Replication of HCV in hepatocytes*

### 1.1.4. Diagnosis of chronic hepatitis C virus

*1.1.4.1. Definition*

CHC is diagnosed when there is evidence of HCV infection for more than 6 months, with or without clinical manifestations, positive anti-HCV and HCV RNA, with or without liver fibrosis/cirrhosis.

*1.1.4.2. Clinical characteristics*

*1.1.4.3. Subclinical characteristics*

Hematological, biochemical, microbiological tests; imaging diagnosis and assessment methods for liver fibrosis/cirrhosis.

## 1.2. LIVER FIBROSIS

### 1.2.1. Pathophysiology of liver fibrosis

### 1.2.2. Degree of liver fibrosis

### 1.2.3. Improvement in liver fibrosis

*1.2.3.1. Mechanism of the improvement of liver fibrosis*

*1.2.2.2. The role of improvement of liver fibrosis and clinical effectiveness*

### 1.2.4. Assessment of liver fibrosis

*1.2.4.1. Liver biopsy*

Liver biopsy is the gold standard for the diagnosis of liver fibrosis. However, this is an invasive technique with the risk of serious complications.

*1.2.4.2. Non-invasive methods*

## 1.3. TREATMENT OF CHRONIC HEPATITIS C VIRUS

### 1.3.1. Goals of antiviral treatment

CHC is considered successfully treated when SVR is achieved. According to AASLD 2014, achieving SVR when HCV RNA level is below the detection limit at 12 weeks or later after treatment discontinuation was considered to be SVR24. After 5 years of follow-up, there were 99.2-99.4% of patients achieving SVR without detectable serum HCV RNA.

### 1.3.2. Treatment indications

Antiviral therapy is indicated for all patients with acute and chronic hepatitis C, except those with end-stage liver disease or other severe conditions having short term survival.

**1.3.3. Direct antiviral drug classes**

*1.3.3.1. NS5A . inhibitors*

*1.3.3.2. NS5B RNA-dependent polymerase inhibitors*

**1.3.4. Specific regimens for genotypes 1 and 6**

**1.3.5. The role of resistant variant**

Approximately 10 - 15% of HCV-1 patients untreated with NS5A inhibitors develop NS5A resistance-associated substitutions (RASs) before the treatment.

**1.3.6. Treatment monitoring**

*1.3.6.1. Pre-treatment assessment*

*1.3.6.2. On-treatment monitoring*

*1.3.6.3. Follow-up after treatment*

*1.3.6.4. Criteria for stopping treatment*

**1.4. Non-Invasive methods for the evaluation of liver fibrosis in the study**

**1.4.1. FIB-4**

**1.4.2. Transient elastography**

*1.4.2.1. Principles*

*1.4.2.2. Application*

*1.4.2.3. Factors influencing measurement results*

*1.4.2.4. Advantages and disadvantages*

**1.4.3. Incorporation of noninvasive techniques for the evaluation of liver fibrosis**

Improving the accuracy as well as the sensitivity in diagnosis and monitoring of liver fibrosis.

**1.5. Treatment regimen used in this research**

SOF/LDV is a fixed-dose combination tablet of ledipasvir and sofosbuvir, which are DAA.

The efficacy of a fixed-dose combination tablet of 90 mg of ledipasvir and 400 mg of sofosbuvir orally once-daily for 12 weeks in adults and adolescents with CHC infected with HCV genotypes 1, 4, 5, and 6, with or without compensated cirrhosis has been proven for both new and re-treatment patients with a high SVR rate, of about 97-99%.

**1.6. Liver Cirrhosis Response After Antiviral Therapy**

In CHC patients, reductions in fibrosis and inflammation following successful antiviral therapy were observed in patients treated with IFN and DAA. The improvement of liver fibrosis was

better in the group treated with DAA when compared to those treated with IFN.

### 1.7. Related studies

#### 1.7.1. In Vietnam

Currently, there have not been many Vietnam's scientific research evaluating the efficacy of SOF/LDV regimens in patients with CHC, especially in the Child-Pugh A group, and the role of non-invasive methods for the assessment of liver fibrosis to predict the likelihood of achieving SVR and the monitoring the improvement of liver fibrosis after antiviral therapy.

#### 1.7.2. In the world

# Chapter 2
# SUBJECTS AND METHODS

## 2.1. SUBJECT STUDY

The study was conducted on 108 out-patients aged more than 18 years, diagnosed with chronic hepatitis C virus, with or without compensated cirrhosis, infected with HCV genotype 1 or 6, treated with a fixed-dose combination tablet of 90 mg of ledipasvir and 400 mg of sofosbuvir for 12 weeks, went to the Infectious Disease Clinic, Thu Duc General Hospital from November 1, 2017 to December 31, 2020.

### 2.1.1. Inclusion criteria

- Those diagnosed with CHC according to the criteria of the Ministry of Health 2021, infected with HCV genotype 1 or 6 that treated with SOF/LDV regimen for 12 weeks.
- Consenting to participate in the study.
- Completing the treatment course and not allergic to any ingredient of the medication.

### 2.1.2. Exclusion criteria

- Decompensated cirrhosis (Child-Pugh B or C)
- Had been treated with regimens with NS5B
- Elevated liver enzymes: > 5 times normal levels.

- Stage 5 CKD (Clcr <30 ml/min)
- Using amiodarone
- Liver cancer or HCC detected during the treatment
- Alcoholism (drinking alcohol > 40 g/day for men and > 20 g/day for women).
- Pregnant women.

**2.2. METHODS**

**2.2.1. Study design**

A prospective study with no control group. All participants receive the treatment.

**2.2.2. Study site and period**

The Infectious Disease Clinic, Thu Duc General Hospital from November 1, 2017 to December 31, 2020.

**2.2.3. Study sample**

The sample size was calculated according to the formula:

$$n \geq \frac{Z^2_{1-\alpha/2} \times p(1-p)}{d^2}$$

The calculated sample size: ≥ 107 patients.

**2.2.4. Study variables**

**2.2.5. Steps to conduct the study**

*2.2.5.1. Selecting patients*

*2.2.5.2. Clinical examination*

*2.2.5.3. Para-clinical examinations*

*2.2.5.5. Treatment regimen*

All patients are treated with the combination therapy of sofosbuvir and ledipasvir for 12 weeks.

*2.2.5.6. Evaluation of response to treatment*

Periodic assessment: clinical, biochemical features and HCV RNA at week 4 after treatment initiation, week 12 and 24 after EOT. Performing abdominal ultrasound and Fibroscan every 12 weeks.

Nonperiodic assessment: side effects of SOF/LDV and acute complications of cirrhosis.

Clinical responses: signs and symptoms.

Viral response: rapid virological response (RVR) and sustained virological response (SVR).

Response to treatment of liver fibrosis

- Response to treatment according to Fibroscan: response when fibrosis staging decreased by ≥ 1 stage according to the criteria of Huang R et al (2020).

- Response to treatment according to FIB-4: according to Ghoneim et al (2020)

**2.2.6. Data analysis**

The data was imported into Excel and processed by STATA 14.

Statistical analysis methods:

- Continuous variables with normal distribution are expressed as mean and standard deviation (X ± SD), comparing 2 means by T-test. Variables with non-normal distribution are expressed as median and interquartile range, comparing 2 medians by Wilcoxon test (of 2 independent or paired groups).

- Subgroup and binary variables are expressed as numbers and percentages, compared by the Chi-squared test.

- Changes in liver fibrosis is a binary variable calculated based on 2 variables: FIB-4 and Fibroscan-based score.

- Using logistic regression model to identify factors related to the treatment of liver fibrosis.

- Results are statistically significant when $p < 0.05$.

**2.3. Study Ethics**

The study was approved by the Biomedical Research Ethics Committee, Hue University of Medicine and Pharmacy, Hue University and Thu Duc General Hospital.

## 2.4. Study flow diagram

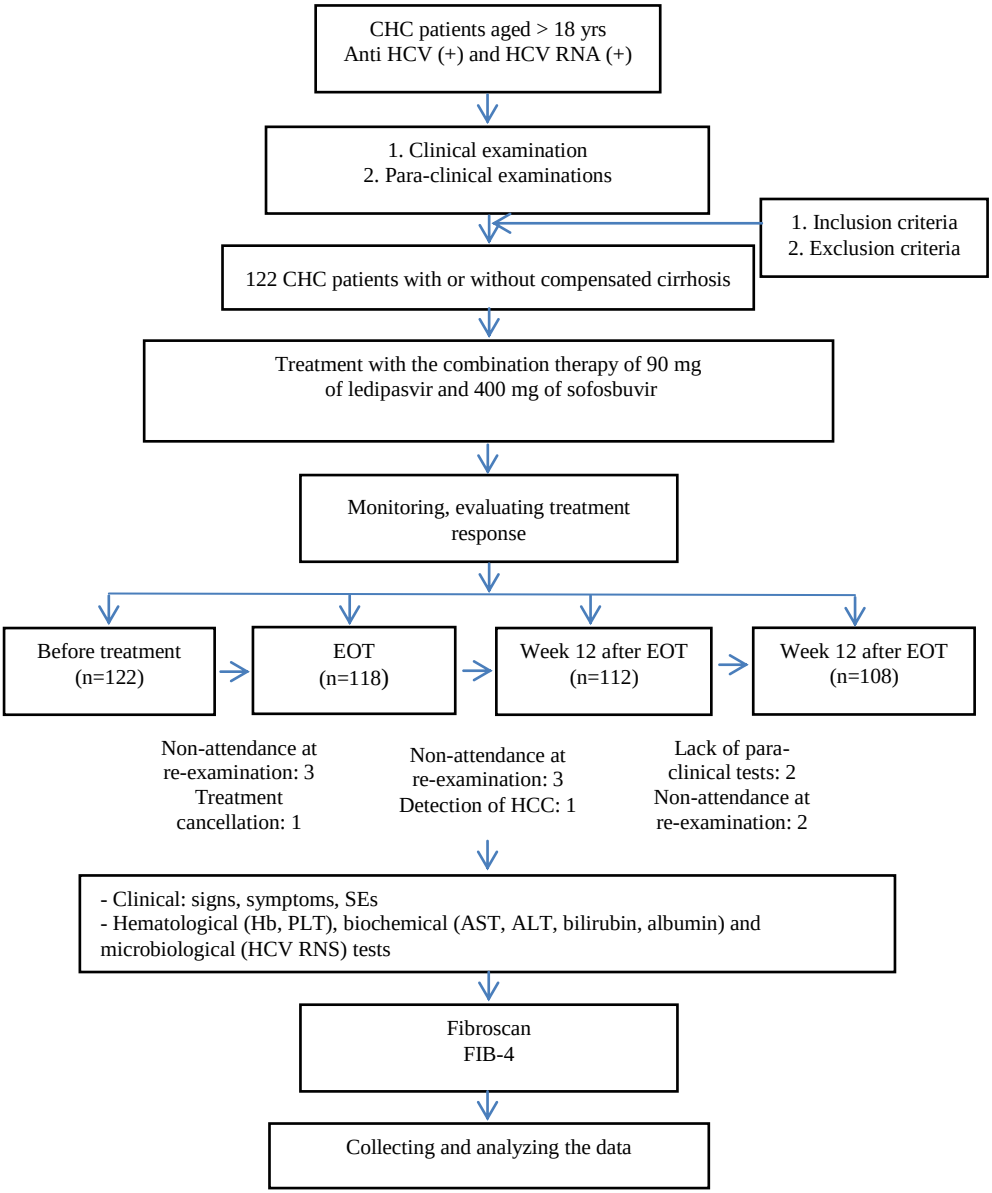


**Figure 2.1.** Study flow diagram

# Chapter 3
# STUDY RESULTS

## 3.1. GENERAL CHARACTERISTICS OF THE STUDY SUBJECTS

### 3.1.1. Age and gender characteristics of study subjects

The percentage of males (63.9%) was nearly 2 times higher than that of females (36.1%). The mean age was 50.2 ± 13.7 years.

### 3.1.2. Clinical characteristics of the patients before treatment

*3.1.2.1. Clinical symptoms before treatment*

Common functional symptoms were fatigue (60.2%), anorexia (45.4%), insomnia (33.3%).

*3.1.2.2. Comorbidity*

The rate of HIV co-infection was 7.4% and 4.6% of patients were co-infected with HBV.

### 3.1.3. Hematological, biochemical and virological characteristics before treatment

*3.1.3.1. Hematological and biochemical characteristics before treatment*

Platelets < 150,000/$mm^3$ accounted for 11.1%; decreased hemoglobin 14.8%; decreased serum albumin (< 3.5 g/dL) 5.6%; increased total bilirubin (>1.0 g/dL) was 10.2%.

*3.1.3.2. AST and ALT activity before treatment*

The median AST and ALT before treatment was 51 U/L and 63 U/L, respectively.

*3.1.3.3. Virological characteristics before treatment*

| HCV characteristics | | n (%) |
|---|---|---|
| HCV RNA Groups | ≥ $4x10^5$ IU/ml | 10 (9.3) |
| | < $4x10^5$ IU/ml | 98 (90.7) |
| Genotypes | 1 | 47 (43.5) |
| | 6 | 61 (56.5) |

**Table 3.5.** Virological characteristics before treatment (n=108)

The mean viral load was 3.3 x x $10^5$ IU/ml (0.99 – 12.9 x $10^5$ IU/ml). The proportion of patients with HCV genotype 6 (56.5%) was higher than genotype 1 (43.5%). The dominant genotypes were 1A, 1B and 6A, 6E.

### 3.1.4. Characteristics of liver fibrosis before treatment

*3.1.4.1. Characteristics of liver fibrosis measured by Fibroscan*

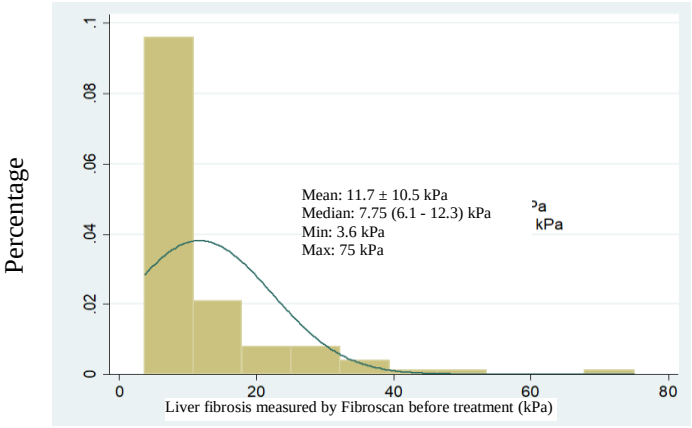


**Diagram 3.3.** Fibroscan values before treatment (n=108)

The pre-treatment Fibroscan values had a non-normal distribution with a median of 7.7 kPa (6.1-12.3 kPa).

The proportion of patients with fibrosis staging evaluated by Fibroscan ≥ 2 (≥ 7.1 kPa) was 59.1%.

*3.1.4.2. Characteristics of liver fibrosis evaluated by FIB-4 index*

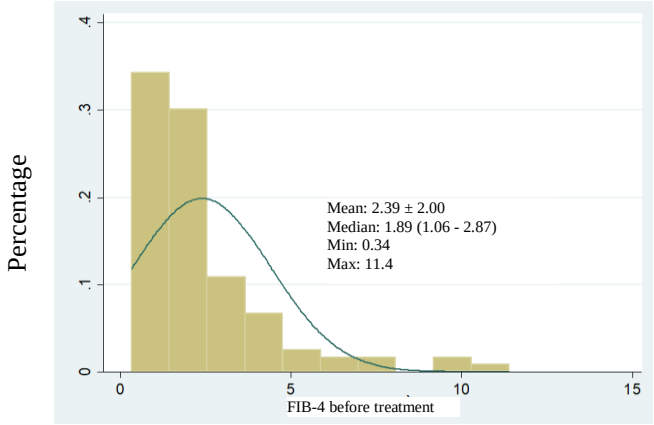


**Diagram 3.5.** FIB-4 scores before treament (n=108)

The pre-treatment FIB-4 values had a non-normal distribution with a median of 1.89 (1.06 – 2.87). The rate of FIB-4 ≥ 1.45 was 62%, there were 21.3% of patients having FIB-4 > 3.25.

### 3.2. ASSESSMENT OF TREATMENT RESPONSE

#### 3.2.1. Clinical response after treatment

*3.2.1.1. The response of clinical symptoms*

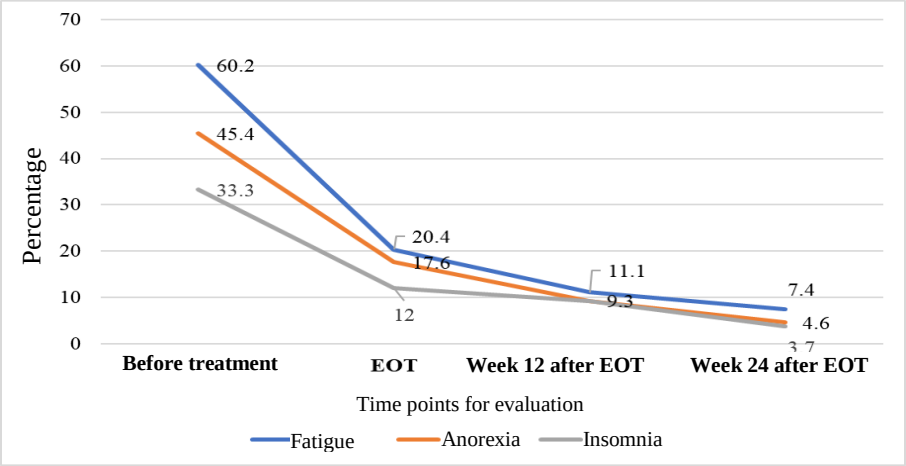


**Diagram 3.7.** *The response of clinical symptoms after treatment*

There was a significant improvement in functional symptoms over time compared with before treatment. Symptoms were most improved at the time of EOT.

*3.2.1.2. Side effects during the treatment*

The two most common side effects were dizziness (18.5%) and headache (13.9%). Less commonly: nausea, loss of appetite, fever. Most were mild and well controlled events. There were no events leading to treatment discontinuation.

*3.2.1.3. Quality of life assessment*

After treatment, the scores of physical health, mental health and overall QoL according to the SF-36 were all increased statistically significantly ($p<0.05$).

### 3.2.2. AST and ALT response

AST and ALT decreased rapidly at the point of EOT, then remained stable at normal levels until week 24 after EOT. The median values of AST and ALT at points of follow-up decreased significantly compared to before treatment ($p<0.001$).

### 3.2.3. Hematological and biochemical responses after treatment

- There was no difference in platelet counts at the points of follow-up compared to before treatment ($p>0.05$).

- There was a gradual increase in albumin levels at the time of EOT, week 12, week 24 compared to before treatment ($p<0.001$).

- The total bilirubin concentration was within the normal range and there was no change during the follow-up ($p<0.05$).

### 3.2.4. Viral response after treatment

**Table 3.13.** Changes in HCV RNA levels after treatment (n = 108)

| | **Week 4 after treatment** | **Week 12 after EOT** | **Week 24 after EOT** |
|---|---|---|---|
| Undetectable HCV RNA | 105 (97.2%) | 107 (99.1%) | 106 (98.1%) |

The percentages of undetectable HCV RNA was 97.2% at 4 weeks after treatment, 99.1% at week 12 after EOT and 98.1% at week 24 after EOT.

**Table 3.14.** Changes in HCV RNA levels after treatment according to fibrosis stages at baseline (n=108)

| **Undetectable HCV RNA** | **Week 4 after treatment** | **Week 12 after EOT** | **Week 24 after EOT** |
|---|---|---|---|
| | n (%) | n (%) | n (%) |
| F0 group | 13 (100) | 13 (100) | 12 (92,3) |
| F1 group | 31 (100) | 31 (100) | 31 (100) |
| F2 group | 24 (100) | 24 (100) | 24 (100) |
| F3 group | 13 (92,9) | 14 (100) | 14 (100) |
| F4 group | 24 (92,3) | 25 (96,2) | 25 (96,2) |

At week 4 after treatment initiation, all patients with fibrosis stage ≥ F2 had undetectable HCV RNA. In patients with cirrhosis (F4), there were 92.3% had an undetectable HCV RNA level at week 4 after treatment and this percentage increased to 96.2% at week 12 after EOT.

### 3.3. ASSESSMENT OF THE IMPROVEMENT OF LIVER FIBROSIS AFTER TREATMENT AND RELATED FACTORS

#### 3.3.1.The improvement of liver fibrosis after treatment evaluated by Fibroscan

**Table 3.15.** The comparison between Fibroscan values

| | **Liver fibrosis scores measured by Fibroscan** | | | |
|---|---|---|---|---|
| | **Pre-treatment** | **EOT** | **Week 12 after EOT** | **Week 24 after EOT** |
| X ± SD | 11.7 ± 10,5 | 10.2 ± 9.1 | 9.6 ± 7.9 | 8.9 ± 7.8 |
| *T-test* | **Baseline** | **EOT** | **SVR12** | |
| EOT | **<0.001** [b] | | | |
| Week 12 after EOT | **<0.001** [b] | **0.045** [b] | | |
| Week 24 after EOT | **<0.001** [b] | **<0.001** [b] | **<0.001** [b] | |

Liver fibrosis scores measured by Fibroscan decreased significantly at EOT, 12 and 24 weeks after EOT compared with before treatment as well as decreased significantly over time between points after treatment ($p < 0.001$).

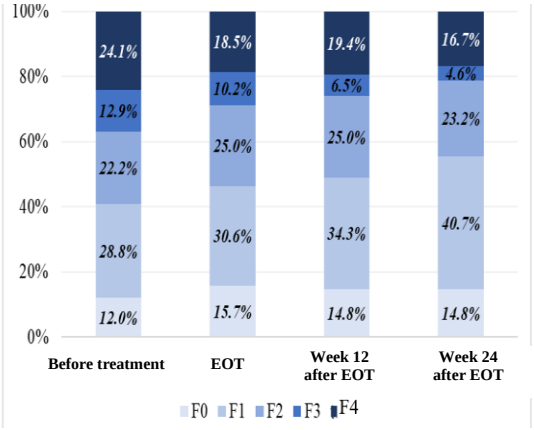


**Diagram 3.8.** The improvement of fibrosis stage according to Fibroscan

There were significant reductions in the proportions of F3 and F4 groups after treatment. Compared with baseline, at week 24 after EOT, the majority were stabilized or decreased at least 1 stage of fibrosis.

### 3.3.2. The improvement of liver fibrosis after treatment evaluated by FIB-4

**Table 3.18.** The comparison between FIB-4 values

| | **Liver fibrosis scores measured by FIB-4** | | | |
|---|---|---|---|---|
| | **Pre-treatment** | **EOT** | **Week 12 after EOT** | **Week 24 after EOT** |
| X ± SD | 2.39 ± 2 | 1.7 ± 1.23 | 1.72 ± 1.38 | 1.72 ± 1.21 |
| *T-test* | **Baseline** | **EOT** | **SVR12** | |
| EOT | **<0.001** [b] | | | |
| Week 12 after EOT | **<0.001** [b] | 0.688 [b] | | |
| Week 24 after EOT | **<0.001** [b] | 0.740 [b] | 0.974 [b] | |

Compared with before treatment, mean values of FIB-4 after treatment decreased significantly (p<0.0001).

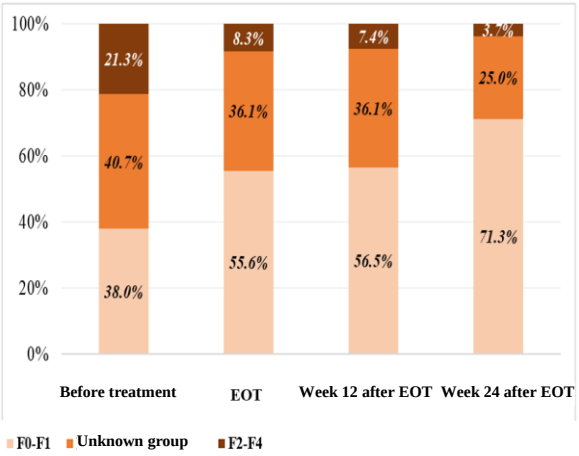


**Diagram 3.9.** FIB-4 groups: before and after treatment

After treatment, there were significant decreases in the percentages of F2-F4 group and the unknown group (decreased by

17.6% and 15.7% at week 24 after EOT when compared to the baseline, respectively).

The majority remained unchanged or regressed ≥ 1 fibrosis stage based on FIB-4. However, increase of fibrosis stage was seen in 2.8% of patients at week 24 after EOT.

### 3.3.3. The rate of liver fibrosis regression after treatment

**Table 3.20.** The rate of liver fibrosis regression after treatment

| Liver fibrosis regression | EOT | Week 12 after EOT | Week 24 after EOT |
|---|---|---|---|
| | n (%) | | |
| According to Fibroscan | 30 (27.8) | 36 (33.3) | 40 (37.0) |
| According to FIB-4 | 32 (29.6) | 34 (31.5) | 27 (25) |
| According to Fibroscan or FIB-4 | 40 (37.0) | 48 (44.4) | 48 (44.4) |
| According to Fibroscan and FIB-4 | 17 (15.7) | 16 (16.8) | 15 (15.8) |

Evaluation by Fibroscan showed a gradual increase in the percentages of liver fibrosis regression at EOT, week 12 and week 24 after EOT (27.8%; 33.3% and 37.0%, respectively).

According to FIB-4, the rate of liver fibrosis regression was highest at EOT (29.6%) and decreased to 25% at week 24 after EOT.

**Table 3.21.** The rate of liver fibrosis regression in the cirrhotic group according to FIB-4 and Fibroscan (n=64)

| Characteristics | Liver cirrhotic (FIB-4 > 3,25 and Fibroscan = F4) | | p |
|---|---|---|---|
| | Yes | No | |
| | n (%) | n (%) | |
| Before treatment | 13 (20.3) | 51 (79.7) | **0.042** |
| Week 24 after EOT | 6 (9.4) | 58 (90.6) | |

The rate of cirrhosis (FIB-4 > 3.25 and Fibroscan = F4) decreased significantly from 20.3% (13 patients) before treatment to only 9.4% (6 patients) at week 24 after EOT ($p<0.05$).

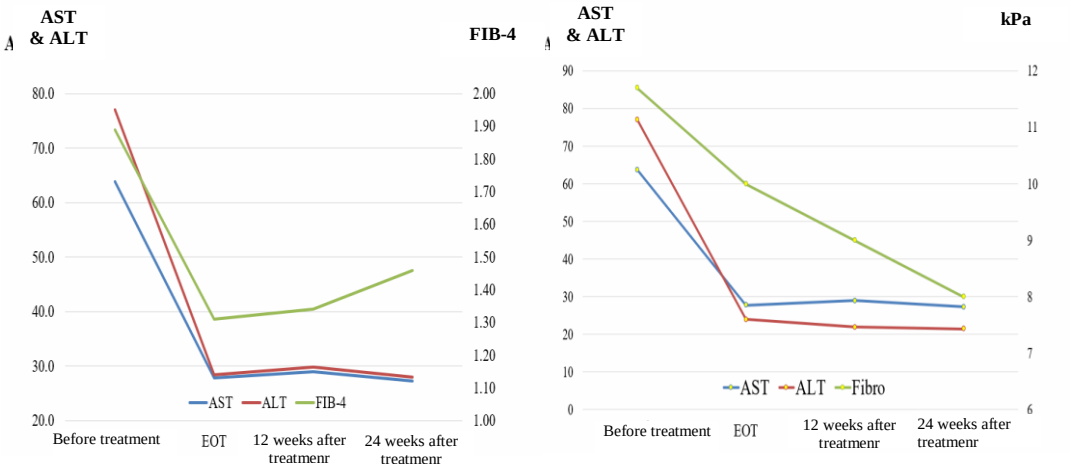


**Diagram 3.10.** Changes in kPa score and FIB-4 according to AST and ALT

The degree of liver fibrosis evaluated by Fibroscan (kPa) decreased steadily at the time of EOT, weeks 12 and 24 after EOT. The FIB-4 index decreased at the point of EOT then stabilized through week 12 and 24 after EOT.

### 3.3.4. Factors related to change in liver fibrosis after treatment

- No associations were found between change in liver fibrosis at week 24 after EOT evaluated by Fibroscan or FIB-4 with genders, age groups ($p>0.05$).

- Among the comorbidities, no associations were found between change in liver fibrosis at week 24 after EOT evaluated by FIB-4 with the comorbidities ($p>0.05$); meanwhile, obesity was associated with poorer change in fibrosis at week 24 after EOT when measured by Fibroscan (15.38% compared to 46.34%; $p<0.05$).

- There were no relationships between liver fibrosis measured by Fiboscan or FIB-4 at week 24 after treatment with PLT, albumin, bilirubin, genotype and HCV RNA level ($p>0.05$).

- Elevated AST or ALT at baseline were both related to the change in liver fibrosis at week 24 after EOT when measured by Fibroscan ($p<0.05$). Meanwhile, only elevated AST was associated with the change in liver fibrosis at week 24 after EOT when evaluated by FIB-4 ($p<0.05$).

- Logistic analysis showed a difference in the rate of fibrosis regression measured by Fibroscan at week 24 after EOT in the baseline fibrosis groups ($p<0.05$): F2 and F3 groups had the rates of liver fibrosis regression measured by Fibroscan at week 24 after EOT higher than that of F1 group ($p<0.05$).

### 3.3.5. Factors related to the change in liver fibrosis through multivariate analysis

**Table 3.31.** Multivariable logistic regression analysis of factors related to the change in liver fibrosis measured by Fibroscan

| Change in liver fibrosis measured by Fibroscan | OR | 95%CI | p |
|---|---|---|---|
| Age group | 0.94 | 0.48 - 1.82 | 0.845 |
| Hypertension | 1.61 | 0.34 - 7.45 | 0.543 |
| Obesity | 0.18 | 0.03 - 1.02 | **0.05** |
| Diabetes | 0.33 | 0.08 - 1.33 | 0.119 |
| AST > 37 U/L | 0.49 | 0.16 - 1.56 | 0.230 |
| ALT > 40 U/L | 0.51 | 0.14 - 1.92 | 0.322 |
| The degree of fibrosis at baseline | 1.27 | 1.02 - 1.99 | **0.022** |

**Table 3.32.** Multivariable logistic regression analysis of factors related to the change in liver fibrosis measured by FIB-4

| Change in liver fibrosis measured by FIB-4 | OR | 95%CI | p |
|---|---|---|---|
| Age group | 1.19 | 0.57 - 2.49 | 0.644 |
| Hypertension | 1.16 | 0.26 - 5.23 | 0.850 |
| Obesity | 0.64 | 0.10 - 3.99 | 0.635 |
| Diabetes | 0.21 | 0.02 - 1.86 | 0.161 |
| AST > 37 U/L | 0.03 | 0.003 - 0.33 | **0.004** |
| ALT > 40 U/L | 2.98 | 0.59 - 14.96 | 0.186 |

Multivariable logistic regression analysis showed that factors related to the change in liver fibrosis according to Fibroscan were obesity and the initial degree of fibrosis ($p<0.05$) while baseline AST > 37 U/L was the only factor that associated with the change in liver fibrosis if measured by FIB-4 ($p=0.003$).

# Chapter 4
# DISCUSSION

## 4.1. GENERAL CHARACTERISTICS OF STUDY SUBJECTS

General characteristics of the patients including age, gender, clinical features, comorbidities as well as biochemical, hematological features and HCV RNA level before treatment were similar to domestic studies and several studies in the world.

In terms of genotype, genotype 6 (56.5%) accounted for the highest percentage. This is consistent with other studies in Vietnam and Southeast Asian countries where genotype 6 is common. However, epidemiological studies have shown that HCV-1 is the most prevalent genotype worldwide with 83.4 million patients (46.2%), about a third of which are in East Asia. Genotype 3 is the second most common genotype globally (54.3 million, 30.1%); genotypes 2, 4 and 6 accounted for a total of 22.8% of cases.

Determining the degree of liver fibrosis such as significant fibrosis or severe fibrosis plays an important role in indicating treatment and screening for complications. Results of the study showed that 59.1% of cases had established fibrosis when evaluated by Fibroscan, the highest proportion was registered by F1 (28.8%), followed by F4 24.0%, F2 22.2% and F3 with 12.9%. These percentages are quite similar to those of domestic studies.

## 4.2. ASSESSMENT OF CLINICAL, HEMATOLOGICAL, BIOCHEMICAL AND VIRAL RESPONSES

### 4.2.1. Clinical response

*4.2.1.1. Changes of symptoms*

Clinical symptoms decreased when patients were treated with the regimen of SOF/LDV at week 24 after EOT, similar to the study of

Tran Tu Oanh (2018) and Ichikawa T et al (2018). SVR achievement leads to the improvement of clinical symptoms.

*4.2.1.2. Quality life before and after value*

The results recorded significant increases in all QoL scores ($p < 0.050$), especially in patients with advanced fibrosis ≥ F3, which is similar to studies conducted in Europe and North America. In Japan, CHC patients treated with RBV showed a slight decrease in QoL while patients treated with SOF/LDV not only received a high efficiency treatment but also improved QoL.

*4.2.1.3. Side effects during the treatment*

Side effects occurred in our study were similar to those of DAA which have been observed from other studies such as the ION-1 study. There were no deaths or treatment discontinuations during the treatment and follow-ups.

**4.2.2. Biochemical response**

AST and ALT decreased rapidly at the time of EOT and remained stable afterwards, this result is similar to other domestic and foreign research.

Bilirubin concentration did not change significantly. The increase in albumin levels after treatment partly showed the effectiveness of DAA regimens in the improvement of liver function among CHC patients.

**4.2.3. Viral response after treatment**

There were good viral responses at 4 weeks after treatment, week 12 and week 24 after EOT. The highest rate of SVR was seen in F4 Group with 96.2%, similar to other studies in the world, of more than 95%. Various studies have demonstrated that HCV genotype and HCV RNA level do not affect SRV achievement; meanwhile, cirrhosis is one of the related factors affecting the rate of SVR.

## 4.3. ASSESSMENT OF THE IMPROVEMENT IN LIVER FIBROSIS AFTER TREATMENT AND RELATED FACTORS

**4.3.1. Changes in liver fibrosis after treatment**

*4.3.1.1. Changes in liver fibrosis after treatment measured by Fibroscan*

The degree of liver fibrosis evaluated by Fibroscan decreased over time, from 1.5 kPa (12.8%) at EOT and continued to decrease by 1.3 kPa (by 11.1%) at week 24 after EOT ($p<0.001$), showing a rapid and early improvement at the end of treatment and afterwards. After treatment, the percentage of fibrosis regression increased gradually over the time points: EOT (27.8%), week 12 (33.3%) and week 24 after EOT (37%), this is consistent with the results of many domestic and foreign studies.

The percentage of patients in group F4 decreased rapidly from 24.1% before treatment to 18.5% at the time of EOT, then decreased to 16.7% at week 24 after EOT. This is consistent with the findings of histological studies and non-invasive methods, showing the reversibility of fibrosis, returning to the non-cirrhotic threshold in CHC patients with prior cirrhosis.

The improvement of fibrosis is different between baseline degrees of liver fibrosis: 92.9% of patients in F1 Group showed the improvement in liver fibrosis while the percentages of regression in F2, F3, F4 Group were 44.2%, 15.1% and 9.3%, respectively.

*4.3.1.2. Changes in liver fibrosis after treatment evaluated by FIB-4*

Values of FIB-4 decreased from 2.39 before treatment to 1.7 at the time of EOT and remained stable at week 12 and 24 after EOT ($p>0.05$), which is similar to other studies in the world.

Many studies have shown that the rapid decrease in fibrosis score after DAA treatment may reflect a decrease in inflammation and is not related to the histological improvement of fibrosis. It is inappropriate to use APRI or FIB-4 to monitor the improvement of fibrosis in patients receiving antiviral therapy. Several studies in patients with CHC have used FIB-4 in screening for HCC or in building models that predict liver histological improvement.

**4.3.2. Factors related to changes in liver fibrosis**

Factors related to liver fibrosis evaluated by Fibroscan were: obesity, baseline levels of AST and ALT and the initial degree of fibrosis. If fibrosis is measured by FIB-4, the only associated factors was level of AST at baseline.

Through regression analysis, different studies recorded different factors related to changes in liver fibrosis, however, generally the two most common factors were BMI (or obesity) and the baseline fibrosis.

Obesity is an associated factor that was recorded in many studies: the improvement of liver fibrosis decreased as BMI increased, especially at week 24 after treatment. Literature also suggests that comorbidities such as obesity, diabetes, or history of alcohol abuse may play important roles in the development of liver disease in patients with SVR.

In our study, there were 11.1% of patients with SVR achievement suffered from fibrosis progression, which similar to Naoki et al (2021) with 11% of patients had no progression at week 96 after achieving SVR. In multivariate analysis, baseline level of Angiotensin 2 and increased in fibrosis stage at week 24 after EOT were associated with no improvement in fibrosis at week 96 post-treatment. Our study had a short follow-up period of only 24 weeks after EOT, however, the degree of fibrosis progression at week 24 after EOT may predict the subsequent improvement in fibrosis to some extent.

## CONCLUSION

Evaluating changes in clinical, biochemical, virological features and liver fibrosis on 108 CHC patients treated with the combination therapy of sofosbuvir 400mg and ledipasvir 90mg for 12 weeks, our study offers the following conclusions:

**1. Evaluation of clinical, biochemical and virological response**

- Symptoms of fatigue (60.2%), anorexia (45.4%) were common before treatment. There was a significant improvement in these symptoms at EOT and thereafter ($p<0.001$).
- The median values of AST and ALT at points of follow-up decreased significantly compared to before treatment ($p<0.001$).
- There was no difference in platelet counts at the points of follow-up compared to before treatment ($p>0.05$).
- There was a gradual increase in albumin levels at the time of EOT, week 12, week 24 compared with before treatment ($p<0.001$).
- The total bilirubin concentration was within the normal range and there was no change during the follow-up ($p<0.05$).

- The rate of virological response at 4 weeks after treatment was 97.2% and SVR12 was 99.1%.

- The most common side effects were dizziness (18.5%), headache (13.9%). There were no events leading to treatment discontinuation.

**2. Evaluation the degree of improvement of liver fibrosis after treatment with related factors**

- The degree of fibrosis measured by Fibroscan decreased over time, from 11.7 kPa before treatment to 10.2 kPa at EOT, 9.6 kPa at week 12 after EOT and 8.9 kPa at week 24 after EOT. The percentage of cirrhosis group was 24.1% before treatment, then decreased to 18.5% at EOT and 16.7 % at week 24 after EOT.

- The degree of improvement of fibrosis measured by Fibroscan gradually increased over time, the rate of regression of fibrosis stage at EOT was 27.8%, then increased to 33.3% at week 12 after EOT and 37% at week 24 after EOT ($p<0.05$). The rates of unchanged and progressed stage of fibrosis were 51.9% and 11.1%, respectively.

- The average value of FIB-4 before treatment was 2.39 and this decreased to 1.70 at EOT, maintained at 1.72 at weeks 12 and 24 after EOT. The percentage of F0-F1 group (<1.45) at the time of pre-treatment was 38.0%, then increased to 55.6% at EOT and 71.3% at week 24 after EOT.

- Factors related to the change in liver fibrosis were: obesity, AST level and the initial degree of liver fibrosis ($p<0.05$).

## RECOMMENDATIONS

- Patients with HCV genotype 1, 6 receiving early treatment should be treated with the combination therapy of sofosbuvir and ledipasvir, especially those with advanced stages of fibrosis or compensated cirrhosis. This helps to achieve the improvement in liver fibrosis in addition to biochemical and viral responses.

- It is recommended that routine assessments of liver fibrosis by Fibroscan or at least the FIB-4 index, preferably a combination of

these two methods, is necessary to monitor changes in liver fibrosis after antiviral therapy in order to plan an appropriate strategy to monitor cirrhosis and HCC complications.

- Larger studies with control group and longer follow-up period are needed, especially for identifying predictors of changes in liver fibrosis.

- In addition, further studies are needed to evaluate the combination of antiviral therapy and other medications (antifibrotic drugs,...) in the improvement of liver fibrosis.

## LIST OF SCIENTIFIC STUDIES RELATED TO THIS THESIS

1. Tran Van Huy, Tran Nguyen Ai Thanh (2019), “Changes in liver fibrosis among patients with chronic hepatitis c virus genotype 1 or 6 treated with the combination therapy of sofosbuvir and ledipasvir", Journal of Medicine and Pharmacy, Hue University of Medicine and Pharmacy; 9 (6), pp. 121 - 125.

2. Tran Van Huy, Tran Nguyen Ai Thanh (2021), "Biochemical and viral response in patients with chronic hepatitis C genotype 1, 6 treated with the combination therapy of sofosbuvir and ledipasvir ", Journal of Medicine and Pharmacy, Hue University of Medicine and Pharmacy; 1 (11), pp. 66-71.