นิพนธ์ต้นฉบับ . Original Article

ผลการรักษาด้วยยา Sofosbuvir ร่วมกับ Peg-Interferon และ Ribavirin ในการรักษาผู้ป่วยไวรัสตับอักเสบซีเรื้อรังชนิด 3 (หลักฐานจากการใช้งานจริง)

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Treatment Outcomes of Sofosbuvir in Combination with Peg-Interferon and Ribavirin in the Treatment of Chronic HCV Genotype 3 (Evidence from Real Clinical Practice)

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บทคัดย่อ

หลักการและวัตถุประสงค์: ยาโซฟอสบูเวียร์ (sofosbuvir) เป็นตัวยับยั้ง NS5B polymerase ซึ่งมีฤทธิ์ยับยั้งการเจริญเติบโตของไวรัสซีได้ทุกสายพันธ์และยากต่อการดื้อยา คณะกรรมการบัญชียาหลักแห่งชาติได้บรรจุยา sofosbuvir เข้ารายการบัญชียาหลักแห่งชาติตั้งแต่ปี พ.ศ. 2561 การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาประสิทธิผลจากการรักษาจริงในโรงพยาบาลจังหวัดกาฬสินธุ์ ซึ่งเป็นจังหวัดที่มีการระบาดของไวรัสซีสูงเป็นอันดับ 3 ในภาคตะวันออกเฉียงเหนือ

วิธีการศึกษา: ในการศึกษานี้ เป็นการวิจัยเชิงพรรณนาเก็บข้อมูลย้อนหลังโดยรวบรวมข้อมูลของผู้ป่วยที่ติดเชื้อไวรัสตับอักเสบซีเรื้อรังสายพันธุ์ 3 ที่มารับการรักษาด้วยยา sofosbuvir 400 มก. รับประทานวันละ 1 ครั้ง ร่วมกับยาเพ็กอินเตอร์เฟียรอน (Pegasys® หรือ Peg-Intron®) ฉีดใต้ผิวหนังสัปดาห์ละครั้ง และยาไรบาไวริน (ribavirin) ตามน้ำหนักตัว 600-1,000 มก. ต่อวัน แบ่งรับประทานวันละ 2 ครั้ง หลังอาหาร เช้า-เย็น ระหว่างเดือนเมษายน พ.ศ. 2562 ถึงกุมภาพันธ์ พ.ศ. 2564 อายุอยู่ระหว่าง 18-70 ปี มีระดับ HCV RNA มากกว่าหรือเท่ากับ 5,000 IU/mL, ค่าผังผืดในตับวัดโดยไฟโบรสแกน (FibroScan®) อย่างน้อย 7.0 kPa ผลลัพธ์หลักคือการตรวจไม่พบไวรัสในเลือดเมื่อ 12 สัปดาห์หลังหยุดการรักษา (SVR 12) ผลลัพธ์รอง คือ ความปลอดภัย, การเปลี่ยนแปลงค่าทางห้องปฏิบัติ เช่น LFT, CBC, ค่าคริเอทีนิน (creatinine)

ผลการศึกษา: จำนวนผู้ป่วย 103 ราย แต่ 1 ราย ไม่ได้ติดตามต่อเนื่อง เหลือผู้ป่วยทั้งหมด 102 ราย อายุเฉลี่ยคือ 52 ± 8 ปี อายุมากที่สุด 70 ปีและอายุน้อยสุด 22 ปี SVR 12 สำหรับ SOF/PEG-IFN/RBV คือ ร้อยละ 100 คิดตาม per protocol อย่างไรก็ตามผู้ป่วย 1 รายเสียชีวิตจากสาเหตุอื่น ๆ และ 1 รายหยุดการรักษาเนื่องจากแจ้งว่ามีอาการแน่นหน้าอกหลังใช้ยา 3 สัปดาห์ โดยเมื่อตรวจโดยละเอียดด้วยคลื่นไฟฟ้าหัวใจ เจาะเลือดระดับโทรโพนิน ที (TNT-T) เอกซเรย์หัวใจ และอัลตราซาวน์หัวใจ ไม่พบความผิดปกติ ทำให้อัตรา SVR12 เป็น 100 จาก 102 ราย (ร้อยละ 98) ไม่มีรายงานผลข้างเคียงรุนแรงจากการใช้ยาดังกล่าว

สรุป: ยาสูตร Sofosbuvir, Peginterferon, และ Ribavirin แม้เพียงขนาด 600 มก. เป็นระยะเวลา 12 สัปดาห์มีการรักษาที่สูงได้ SVR12 เกือบร้อยละ 100 ในผู้ป่วยไวรัสตับอักเสบซีเรื้อรังสายพันธุ์ 3 ในประเทศไทย ผู้ป่วยเกือบทั้งหมดสามารถใช้ยาได้จนครบตามตำรับยา และมีความปลอดภัยสูง

คำสำคัญ: โซฟอสบูเวียร์, เพ็กอินเตอร์เฟียรอน, ไรบาไวริน, ไวรัสตับอักเสบซีสายพันธ์ 3

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Abstract

Background and Objective: Sofosbuvir is a nucleotide based NS5B polymerase inhibitor that exhibits PAN genotypic antiviral activity and has a high genetic barrier. This drug has been included in reimbursed universal health coverage in Thailand since 2018. The aim of this study was to report the results of this regimen in real life in Kalasin province, which has the third highest prevalence of HCV in Northeastern Thailand

Methods: In this retrospective descriptive study, patients with chronic HCV genotype 3 were recruited to receive triple therapy with sofosbuvir 400 mg once a day, plus Peg-interferon (either Pegasys® or Peg-Intron®) administered through subcutaneous injection weekly, and weight-based ribavirin (600-1,000 mg) daily, divided into 2 doses, one after breakfast and one in the evening. All patients were enrolled between April 2019 and February 2021, and were eligible for inclusion if they were aged 18–70 years, had an HCV RNA level of 5,000 IU/mL or greater, and had a liver stiffness measurement of ≥ 7.0 kPa as assessed by Fibroscan®. The primary outcome was sustained virologic response at 12 weeks after discontinuation of antiviral drugs (SVR12). Secondary outcomes included safety, tolerance, and changes in laboratory values such as LFT, CBC, and creatinine.

Results: The study initially enrolled 103 patients. However, one patient did not comply with the protocol, resulting in a total of 102 patients available for analysis. The mean age was 52 ± 8 years old. The oldest patient was 70 years old, and the youngest was 22 years old. The SVR12 for SOF/PEG-IFN/RBV was 100%. However, one patient died due to an event unrelated to treatment, and another discontinued early due to chest discomfort that was not associated with the regimen. Resulting in an SVR12 rate of 100 out of 102 patients (98%) per intention to treat. No serious adverse events were reported in this study.

Conclusion: The combination of Sofosbuvir, Peg-interferon, and even a low dose of Ribavirin (600 mg) for 12 weeks was highly efficacious, achieving an SVR12 rate of nearly 100% in Thai patients infected with genotype 3 HCV. This regimen was well-tolerated with excellent safety profiles.

Keywords: Sofosbuvir, Peg-Interferon, Ribavirin, HCV genotype 3

Introduction

The hepatitis C virus (HCV) infection remains a significant cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma. As of early 2020, there were an estimated 56·8 million viremic HCV infections globally[1]. The prevalence of HCV in Thailand has raised concerns among healthcare providers and policymakers, with an estimated 1-2% of the Thai population living with chronic HCV.[2,3] In Kalasin province, which has the third highest prevalence (5.29%) of HCV in Northeastern Thailand[4], the major risk factors for HCV infection were needle sharing, tattoos, men sex with men (MSM) and people who inject drugs (PWID). The WHO aims to eliminate HCV by 2030. To achieve this goal, Thailand was improved screening and healthcare coverage to eradicate HCV. Before the introduction of direct-acting antiviral (DAA) agents, the standard treatment for HCV involved a combination therapy of Peg-interferon (Peg-IFN) and ribavirin (RBV). However, this regimen was associated with numerous adverse effects and limited success rates in achieving sustained virological response at 12 weeks (SVR12), ranging from 40% in genotype 1 (GT1) to 60-80% in genotypes 2 or 3 (GT2 or GT3).[5,6]

Since 2018, sofosbuvir (SOF) has been available in Thailand's government health system. Previously, HCV patients in Kalasin had to be transferred to Khon Kaen due to a shortage of gastroenterologists. This not only increased costs for patients due to transportation and some drug expenses but also caused inconvenience. However, starting from 2018, HCV patients in Kalasin can now receive treatment locally. I initiated targeted treatment for HCV GT3 by utilizing a 12-week combination therapy consisting of SOF, Peg-IFN, and RBV, in accordance with the Thailand Practice Guideline for Management of Chronic Hepatitis C 2018[7]. At that time, the combination of sofosbuvir/velpatavir (SOF/VEL) was not yet available in Thailand. SOF/VEL, which possesses PAN genotypic activity, high efficacy, and very low adverse events, was introduced in the country in the year 2022. This study aims to study the real clinical practice outcomes in Kalasin Provincial Hospital.

Materials and Methods

In this retrospective descriptive study, all GT3 HCV patients were recruited between April 2019 and February 2021 at Kalasin Hospital, the secondary care hospital in Kalasin province. Data from all medical records were analyzed using descriptive statistics. The inclusion criteria were patients who were aged between 18 and 70 years, had HCV VL ≥ 5,000 IU/mL, showed significant liver fibrosis (≥F2) determined by Fibroscan® (Echosens, France) ≥ 7.0 kPa, had abstained from alcohol for more than 6 months, had a Child-Turcotte-Pugh (CTP) score < 10, GFR ≥ 30 ml/min, no pregnancy, and no active underlying disease or malignancy. All patients were treated with sofosbuvir 400 mg once a day, plus either Peg-IFN alfa-2a at a dose of 180 mcg (Pegasys®) or Peg-IFN alfa-2b (Peg-Intron®) at a dose of 1.5 mcg/kg administered through weekly subcutaneous injection, plus weight-based ribavirin (600-1,000 mg) daily, divided into 2 doses, one after breakfast and one in the evening, for a duration of 12 weeks. The interval for follow-up depended on the patients' well-being and varied from 4 to 6 weeks intervals. Details on patients in the study are displayed in Figure 1.

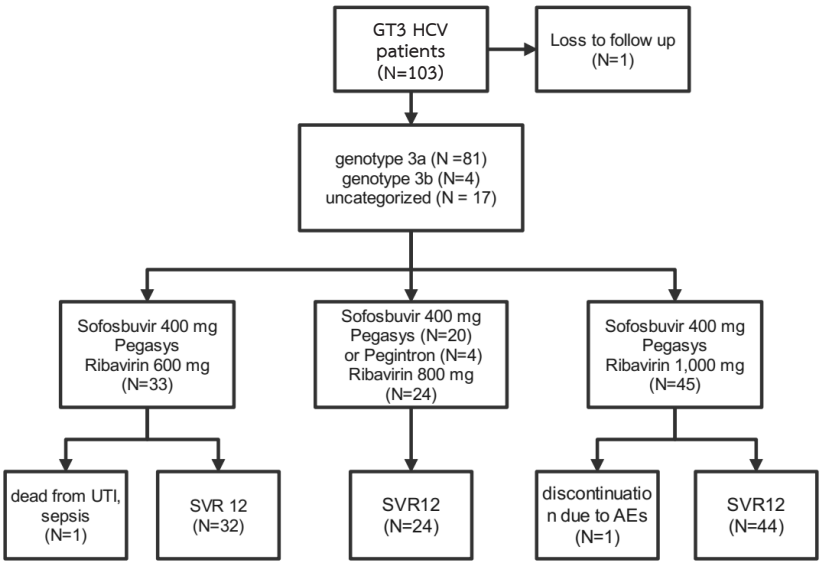

Figure 1 patient disposition.

Assessment of severity of liver disease

Liver fibrosis stage was determined using ultrasound-based vibration controlled transient elastography (VCTE; Fibroscan®). According to the Thailand practice guidelines for the management of chronic hepatitis C 2018[7], the cutoff for F2 fibrosis was ≥ 7.0 kPa. In this study, the cutoff for F4 fibrosis or cirrhosis was 13.0 kPa.[8] Liver function test (LFT) and basic laboratory tests, such as complete blood count (CBC), blood urea nitrogen (BUN), and creatinine (Cr), were collected at baseline. Ultrasound examinations were performed on all patients.

Demographic and laboratory data collection

Baseline demographic data such as age, gender, height, weight, body mass index, and laboratory parameters including LFT, BUN, Cr, CBC, HCV viral load (HCV VL), and genotype were recorded at the initial visit (Table 1). Subsequently, LFT, BUN, Cr, and CBC were recorded at follow-up appointments. The diagnosis of liver cirrhosis was established through clinical evaluation, biochemical tests, Fibroscan®, and ultrasonography. The HCV genotype was identified using the VERSANT HCV Genotype 2.0 Assay (LiPA), which has the capability to detect HCV genotypes 1 to 6 and subtypes a and b of genotype 1 in both human serum and EDTA plasma samples. However, there is a limitation in determining the HCV genotype, as the HCV viral load must be above 2,106 IU/mL to ensure accurate results. To measure the levels of HCV RNA in the serum, the Abbott Realtime HCV assay was utilized. This assay employs the in vitro reverse transcription polymerase chain reaction (RT-PCR) technique and is specifically designed for use with the Abbott m2000sp and m2000rt instruments. The Abbott Realtime HCV assay has a detection limit of 12 IU/mL. The outsourcing of this assay was carried out through a laboratory service known as PCT Lab.

HCV RNA quantification took place at baseline and was repeated at week 12 (SVR12) after the completion of therapy. Secondary outcomes included analyzing factors associated with SVR12 and evaluating treatment-related adverse events (AEs).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows (Version 28.0.1 Armonk, NY: IBM Corporation) Demographic data and baseline characteristics were analyzed using descriptive statistics. Variables were compared using the independent t-test, categorical variables were compared using the Chi-square test. Multivariate associations between the baseline demographic data, biochemical, viral factors, and SVR12 were determined using Cox regression analysis. All statistical data were two-tailed, with a p-value <0.05 considered statistically significant.

Ethical Concern

All collected data were kept anonymously and confidentially. The study received approval from the research ethical committee of Kalasin hospital, KLSH REC No.034/2023R.

Results

Medical records from 103 patients were retrieved. One patient was lost to follow-up, leaving a total of 102 patients for analysis in this study. Males accounted for 64.7% (66 patients) and the mean age was 52.3 ± 8.0 years. A high baseline viral load, defined as HCV RNA > 6,000,000 IU/mL, was noted in 7 patients (6.9%). Overall, 67.6% (69 patients) had cirrhosis defined by F4 fibrosis, and most of these were compensated (CTP Class A 83.1% and CTP Class B 16.9%). A total of 2 patients (1.96%) had prior treatment experience. The most common comorbidities were diabetes mellitus for 10 patients, HIV coinfection for 8 patients, and HBV coinfection for 6 patients, respectively. Out of these 102 patients, one experienced treatment discontinuation after 3 weeks due to complaint of chest tightness that was unrelated to the regimen, despite their unwillingness to continue the regimen. Further echocardiogram results showed mild mitral regurgitation, mild pulmonary hypertension, and an ejection fraction of 76%. Another patient, who had cirrhosis CTP Class B before starting the regimen, succumbed to a urinary tract infection (UTI) with methicillin-resistant Staphylococcus epidermidis (MRSE) septicemia after 8 weeks of treatment. In the end, 100 out of the 102 patients who completed the regimen achieved SVR12, even though 1 in 100 received only a 9-week duration, resulting in a 100% SVR in per-protocol analysis. One patient received a reduced dose of Pegasys (0.4 mL) in week 5 due to anemia, and another patient deferred Pegasys for 1 week; both achieved SVR12. Apart from SVR12, the biochemical tests indicate improvement, with a decrease in APRI of -41.9 ± 33.7 and Fib-4 of -11.9 ± 34.3. (Table 2) The correlations between factors revealed that viral load decreases with age. APRI and Fib-4 are correlated with age. Additionally, APRI is correlated with fibrosis and Fib-4. Multivariate regression analysis did not show any factor was associated with SVR12.

No serious adverse events were reported. Fatigue was the most reported symptom during treatment, followed by anemia. Temporary discontinuation of the medication for 1-2 weeks was implemented, and subsequent visits demonstrated an improvement in anemia, allowing the resumption of the regimen.

Discussion

In this real-world study, the combination of SOF/Peg-IFN/RBV demonstrated high effectiveness in treating HCV genotype 3 (both 3a and 3b), achieving 100% SVR12 rate according to the per protocol analysis. This success was achieved even with a low dose of ribavirin (600 mg), which is comparable to findings in previous studies.[9,10] The observed effectiveness remained consistent regardless of variables such as gender, age, age groups, HCV viral load, fibroscan value, fibrosis stage, or ribavirin dose. However, it is important to note that this study was not specifically designed to identify factors predicting SVR12 achievement. Therefore, the sample size may

not be sufficient to conclusively address this question. While these treatment regimens are no longer commonly used in Thailand, the current standard regimen is Sofosbuvir/Velpatasvir (SOF/VEL) due to its high efficacy, cost-effectiveness, and minimal adverse events. However, SOF/Peg-IFN/RBV may still be considered as an option in certain countries or potentially in Thailand in the future, as some patients have failed the combination of SOF/VEL/RBV. Further studies are needed to determine the role of this regimen as a salvage treatment for refractory HCV genotype 3, which represents a small subset of patients who did not achieve SVR12 with SOF/VEL or SOF/VEL/RBV treatment.

Also, this study has demonstrated that a low dose of RBV (600 mg) can lead to SVR12 in HCV genotype 3. Additional research on the efficacy of SOF/VEL/low dose RBV (600 mg) for genotype 3 or other genotypes is warranted to further investigate this question.

Conclusion

The combination of Sofosbuvir, Peg-interferon, and even a low dose of Ribavirin (600 mg) for 12 weeks was highly efficacious, achieving an SVR12 rate of nearly 100% in Thai patients infected with genotype 3 HCV. This regimen was well-tolerated with excellent safety profiles.

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Table 1 Demographic of patients

Parameters	N (%)
Age (years), mean ± SD	52.3 ± 8.0 (22-70)
Gender (male vs female) (% male)	66 vs 36 (64.7% male)
Genotype	
3a	81 (79.4)
3b	4 (3.9)
3 (unclassified)	17 (16.7)
High Viral Load (IU/mL)	
≥ 6,000,000	7 (6.9)
< 6,000,000	95 (93.1)
Fibrosis Score (F2-4)	
F2-F3	32 (31.4)
F4	70 (68.6)
CTP A 5-6	60
CTP B 7	8
CTP B 8	1
CTP B 9	1
Prior treatment history	
Treatment naïve	100
Treatment experience	2
Fibrosis (kPA), mean ± SD.	
Male	27.8 ± 18.6
Female	22.4 ± 14.6

Table 2 Laboratory parameters before treatment compare with SVR12.

	Before treatment	SVR12
Hb (g/dL), mean ± SD	13.2 ± 1.7	13.0 ± 1.9
WBC (/mm3), mean ± SD	6,399 ± 2,040	5,733 ± 1,879
Platelet (x10^9/L), mean ± SD	149.5 ± 61.5	149.3 ± 65.2
% PMN (mean ± SD, range)	45.8 ± 11.2 (19.1-70.7)	46.3 ± 11.5 (19.3-68.6)
% Lymphocyte (mean ± SD, range)	38.8 ± 11.9 (14.2-73.5)	38.3 ± 11.6 (13.0-70.8)
% Monocyte (mean ± SD, range)	9.2 ± 2.8 (1-15.9)	8.9 ± 3.0 (1.0-16.3)
% Eosinophil (mean ± SD, range)	6.2 ± 9.6 (0.3 -90)	5.6 ± 5.3 (0.5-24.0)
Creatinine	0.9 ± 0.2 (0.5-1.8)	0.9 ± 0.2 (0.5-1.7)
Total protein (g/dL)	7.9 ± 0.6 (6.6-9.3)	7.8 ± 0.8 (4.4-10.1)
Albumin (g/dL)	3.6 ± 0.5 (2.4-4.7)	3.8 ± 0.6 (2.4-4.8)
TB (mg/dL), median (mg/dL)	1.07 ± 0.65 (0.35-3.74)	0.89 ± 0.70 (0.30-5.05)
DB (mg/dL), median (mg/dL)	0.31 ± 0.29 (0.02-1.59)	0.23 ± 0.29 (0.01-1.95)
AST (U/L), median (U/L)	103.6 ± 59.0 (27.9-348.0)	49.0 ± 27.9 (14.0-216.0)
ALT (U/L), median (U/L)	92.9 ± 54.8 (17.5-304.0)	32.7 ± 17.5 (8.0-99.0)
AP (U/L), median (U/L)	115.4 ± 51.1 (55.0-363.0)	98.6 ± 42.6 (35.0-255.0)
APRI	2.01 ± 1.67 (0.3-9.2)	1.02 ± 0.92 (0.1-4.8)
Fib-4	5.01 ± 4.12 (0.3-24.5)	4.16 ± 3.50 (0.5-21.0)
% APRI change at SVR12	-41.9 ± 33.7 (-86.3 to 93.3)	
% Fib-4 change at SVR12	-11.9 ± 34.3 (-66.7 to 116.4)	

BMI: Body mass index; HCV: Hepatitis C virus

CTP: Child-Turcotte-Pugh

PMN: Polymorphonuclear

TB: Total bilirubin; DB: Direct bilirubin

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; AP: Alkaline phosphatase

INR: International normalized ratio.

Table 3 Difference ribavirin dose groups

Ribavirin dose	600 mg (N=33)	800 mg (N=24)	1,000 mg (N=45)
Body weigt (Kg) ± SD	64.114.4 ± 14.4	58.0 ± 9.2	62.5 ± 9.6
F2	2	7	12
F3	1	3	6
F4	30	14	26
Fibroscan (Mean ± SD)	37.8 ± 17.1	21.5 ± 14.4	19.7 ± 14.9
SVR12	32 (1 dead)	24	44 (1 discontinue)

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