Treatment Outcomes in the Management of Patients with Chronic Hepatitis C: Case Series of Faculty of Medicine Vajira Hospital, Navamindradhiraj University

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Abstract

Objectives: To assess treatment outcomes of different treatment options in the management of patients with non-cirrhotic chronic hepatitis C (CHC) and hepatitis C virus-related compensated cirrhosis at Faculty of Medicine Vajira Hospital, Navamindradhiraj University

Methods: Retrospective study of 54 cases were diagnosed between 1989 and 2011. Forty-nine cases with sufficient data were enrolled into the study. Main outcome measured is efficacy of treatments, including sustained virological response (SVR), end-of-treatment response (ETR), virological relapse, progression to cirrhosis and progression to hepatocellular carcinoma. The adverse events of treatments were reported.

Results: The prevalence of CHC genotype included in the study was genotype 1 in approximately 46.6%. There was no difference in genotype allocation between pegylated interferon alfa-2a and alpha-2b groups. The number of patients that received pegylated interferon alfa-2b was higher than those received pegylated interferon alfa-2a (61.2% vs 36.7%). A higher proportion of patients who received pegylated interferon alfa-2b was observed in non-cirrhotic CHC group (64.9% vs 32.4%). In this study, 85.7% of patients (42/49) completed treatment course. Overall, 88.4% achieved end-of-treatment virological response. The result was not significantly different between cirrhotic and non-cirrhotic groups. End of treatment virological response was achieved in greater than 90% in those received pegylated interferon alfa-2a irrespective of cirrhotic stage. In this study, viral relapse was found in 8 patients (8/38, 21.05%) and most of relapsed cases (6/8, 75%) were associated with advance fibrosis or compensated cirrhosis. Patients completed the courses of treatment had significantly lower rate of disease progression to compensated cirrhosis (4.44% vs 28.57%, $p < 0.05$), and to hepatocellular carcinoma (2.74% vs 28.57%, $p < 0.01$).

Conclusion: Successful treatment outcomes were found in the management of chronic hepatitis C with the standard treatment of pegylated interferon alfa and ribavirin. This study provided useful information about treatment paradigms, treatment outcome and disease progression in the CHC patients in Vajira Hospital.

Keywords: chronic hepatitis C, treatment outcomes, virological response, virological relapse

ผลการรักษาของผู้ป่วยไวรัสตับอักเสบซีเรื้อรังในคณะแพทยศาสตร์วชิรพยาบาล มหาวิทยาลัยนวมินทราธิราช

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บทคัดย่อ

วัตถุประสงค์: ศึกษาผลการรักษาด้วยยาในกลุ่มผู้ป่วยไวรัสตับอักเสบซีเรื้อรังที่ไม่มีภาวะตับแข็งและที่มีภาวะตับแข็งระยะแรก ในคณะแพทยศาสตร์วชิรพยาบาล มหาวิทยาลัยนวมินทราธิราช

วิธีดำเนินการวิจัย: เก็บข้อมูลจากการรักษาจริงในผู้ป่วยไวรัสตับอักเสบซีเรื้อรัง 54 ราย ที่เข้ารับการรักษาระหว่างปี พ.ศ. 2532–2554 ประกอบด้วย ชนิดของยาที่ใช้ในการรักษา ปริมาณไวรัสก่อนและหลังการรักษา การกลับเป็นซ้ำ การเกิดตับแข็งและการเกิดมะเร็งตับหลังการรักษา โดยตัวชี้วัดที่สำคัญได้แก่ ประสิทธิภาพของการรักษาประกอบด้วย การตอบสนองของไวรัสเมื่อสิ้นสุดการรักษา การตอบสนองของไวรัสที่ 6 เดือนหลังการรักษา การกลับเป็นซ้ำของไวรัสหลังการรักษา การเกิดตับแข็งและมะเร็งตับหลังการรักษา

ผลการวิจัย: ผู้ป่วยไวรัสตับอักเสบซีเรื้อรังทั้งหมด 49 ราย พบว่าเป็นไวรัสตับอักเสบซีชนิดสายพันธุ์ที่ 1 ร้อยละ 46.6 โดยไม่มีความแตกต่างระหว่างชนิดสายพันธุ์ไวรัสในกลุ่มผู้ป่วยที่ได้รับยาฉีด pegylated interferon alfa-2a และ pegylated interferon alfa 2b มีกลุ่มผู้ป่วยที่ได้รับยาฉีด pegylated interferon alfa-2b มากกว่า pegylated interferon alfa-2a (ร้อยละ 61.2 และ 36.7) และผู้ป่วยที่ได้รับยาฉีด pegylated interferon alfa-2b ส่วนใหญ่เป็นกลุ่มผู้ป่วยที่ไม่มีตับแข็ง (ร้อยละ 64.9 และ 32.4) จากผู้ป่วยทั้งหมด 49 ราย มีผู้ป่วย 42 ราย หรือร้อยละ85.7 ที่ได้รับการรักษาครบตามเกณฑ์ และในกลุ่มนี้ร้อยละ 88.4 ได้ผลตอบสนองโดยไม่พบปริมาณไวรัสเมื่อสิ้นสุดการรักษา ผู้ป่วยมากกว่าร้อยละ 90 ในกลุ่มที่ได้รับยา pegylated interferon alfa-2a มีการตอบสนองที่ดีโดยไม่พบปริมาณไวรัสเมื่อสิ้นสุดการรักษา สำหรับกลุ่มที่ไม่มีตับแข็งและกลุ่มที่มีตับแข็งระยะเริ่มแรกหากได้รับการรักษาครบตามเกณฑ์ ไม่พบว่ามีความแตกต่างกันอย่างมีนัยสำคัญของการตอบสนองของไวรัสเมื่อสิ้นสุดการรักษา นอกจากนี้พบการกลับเป็นซ้ำของไวรัสหลังการรักษาในผู้ป่วย 8 ราย หรือร้อยละ 21.05 ซึ่งร้อยละ 75% ของจำนวนนี้เป็นกลุ่มที่มีพังผืดปริมาณมากหรือมีตับแข็งระยะแรก ผู้ป่วยที่ได้รับการรักษาครบตามเกณฑ์จะมีอุบัติการณ์การเกิดโรคตับแข็งและมะเร็งตับน้อยกว่ากลุ่มที่ไม่ได้รับการรักษาครบตามเกณฑ์อย่างมีนัยสำคัญ (ร้อยละ 4.44 และ 28.57; $p<0.05$ และร้อยละ 2.74 และ 28.57; $p < 0.01$ ตามลำดับ)

สรุป: ผลการรักษาผู้ป่วยไวรัสตับอักเสบซีเรื้อรังในคณะแพทยศาสตร์วชิรพยาบาล มหาวิทยาลัยนวมินทราธิราช ด้วย pegylated interferon และ ribavirin มีประสิทธิภาพที่ดี และสามารถลดอุบัติการณ์เกิดโรคตับแข็งและมะเร็งตับได้

Introduction

Hepatitis C virus (HCV) infection is a worldwide disease occurring among persons of all age, gender, races and regions of the world. The HCV is a major public health problem and a leading cause of chronic liver disease. Once cirrhosis is established, the rate of developing hepatocellular carcinoma (HCC) is at 1%–4% per year. HCV-related end-stage liver disease and HCC have become the leading cause for liver transplantation worldwide.

In Thailand, the prevalence of HCV among persons screened as potential blood donors in northern Thailand increased from 1.5% in 1992 to 2.8% in 1998. Other studies of volunteer blood donors throughout Thailand have found HCV prevalence rates between 1.5% and 5.0%. Chronic hepatitis occurs in more than 50% of HCV-infected patients, and can lead to cirrhosis and liver cancer. Factors associated with disease progression include duration of infection, age at time of acquirement of infection, gender, alcohol consumption, immunosuppression (e.g., HIV co-infection or organ transplant recipients), obesity, insulin resistance, co-infection with other viruses, elevated aminotransferases and genetic factors. Patients with HCV-related liver cirrhosis have 1.4%-6.9% risk of developing HCC per year. In Thai population, median survival for patients with HCV-associated HCC was only 5.5 months. Morbidities and premature death resulting from chronic hepatitis C (CHC) disease progression cause a significant burden to the patients, healthcare providers, payers and the society.

The current recommended therapy of chronic HCV infection is the combination of a pegylated interferon alfa and ribavirin. The studies from Asia provided evidence to support the same broad treatment strategies for Asian patients as recommended in Western countries. Nevertheless, there is increasing evidence that Asians have a higher likelihood of achieving a sustained virological response (SVR) than their Caucasians counterparts when treated with the corresponding regimen. The goal of therapy is to prevent complications and death from HCV infection. The primary goal of treatment for CHC is a sustained virological response (SVR), defined as the absence of HCV RNA from serum at the end of 24-week follow-up after cessation of therapy. Achieving the endpoint of SVR has been associated with persistent regression of hepatic fibrosis, reduced incidence of cirrhosis, HCC and liver-related mortality. Undetectable virus at the end of either a 24-week or 48-week course of therapy is referred to as an end-of- treatment response (ETR). With the advent of successful therapy for hepatitis C, factors associated with treatment outcome have been increasingly received attention. Factors that can influence treatment success include genotype, age, gender, stage of liver disease, baseline hepatitis C viral load, and prior treatment failure. In particular, advanced liver disease, characterized by bridging fibrosis on biopsy and clinically with the manifestations of cirrhosis, is associated with a worse treatment outcome. Additionally, hepatitis C genotype 1 is substantially more difficult to treat compared with genotypes 2 and 3. Data from various clinical trials suggested that patients with different ethnicities and conditions may vary in their response to interferon-based therapy.

Current recommendations for treatment of patients with chronic HCV infection were derived from data collected in the randomized controlled trials. The management and treatment considerations for patients should be made on a case-by-case basis, taking into consideration the experience of the practitioner together with the acceptance of risk by the patient. While the efficacy of pegylated interferon alfa and ribavirin has been proven by randomized controlled trials, the effectiveness of such therapy has not been investigated in Thailand. The purpose of this observational study is to assess treatment outcomes of different treatment options in the management of patients with CHC at Faculty of Medicine Vajira Hospital, Navamindradhiraj University.

Objectives

To assess treatment outcomes of different treatment options in the management of patients with non-cirrhotic CHC and HCV-related compensated cirrhosis at Faculty of Medicine Vajira Hospital, Navamindradhiraj University

Number of Subjects

The target sample size was approximately 60 subjects. Due to limitation of case number, the timeline for CHC diagnoses were changed from between 2000 and 2010 to 1989 and 2011. Fifty four cases were diagnosed. Forty nine cases with sufficient data were enrolled into the study.

Diagnostic and Main Criteria

Inclusion criteria

Subjects diagnosed with CHC between year 1989 and 2011 were categorized into either one of the following health states.

1) Non-cirrhotic CHC: Subjects were included in non-cirrhotic CHC cohort if they were newly diagnosed with CHC without the evidence of cirrhosis and HCC, and if follow-up data within 6 months after diagnosis was available. CHC was defined by the following diagnostic criteria:

- Antibody to HCV (Anti-HCV) was positive by enzyme immunoassay or confirmatory testing (i.e. RIBA) or HCV RNA was positive by RT-PCR
- RIBA yielded intermediate result with positive RT-PCR or abnormal ALT

2) HCV-related compensated cirrhosis: Subject were included in the HCV-related compensated cirrhosis cohort if they were newly diagnosed with HCV-related compensated cirrhosis (by biopsy, ultrasound or clinical signs such as portal hypertension) without evidence of decompensated cirrhosis and HCC and if follow-up data within 6 months after diagnosis was available.

Exclusion criteria

- Subject who was recruited in other clinical trial
- Subject with Hepatitis B virus co-infection
- Subject with clinical or known acute Hepatitis A virus or Hepatitis D virus
- Subject with known HIV infection
- Subject with known severe medical conditions that were contraindicated to HCV treatment

Criteria for Evaluation

- Efficacy
  - Sustained virological response (SVR)
  - End-of-treatment response (ETR)
  - Virological relapse
  - Progression to cirrhosis
  - Progression to HCC
- Safety: This is a post-marketing study of treatment outcomes associated with CHC and related complications with the treatment regimen per the physician's discretion. Responsibility for clinical follow-up resides with the prescribing physician. Therefore, reporting of AEs and SAEs as they occur in clinical practice followed the established procedures for approved, marketed drugs in compliance with applicable laws and regulations. This applies to AEs and SAEs noted by the prescribing physician through clinical observation, laboratory tests, diagnostic procedures or other applicable methods

Statistical Methods

The level of statistical significance for all analyses was set at 0.05. Descriptive statistics were utilized to describe demographics of subjects and treatment outcomes among different treatment options. The comparison of treatment outcomes among different treatment options were performed by comparing the defined proportions. The analysis was separately conducted for each of the health states. All analyses were performed using SAS version 9.1.3 (SAS Statistical Software; SAS Institute, Inc; 2007; Cary, NC, USA).

Methodology

This is a retrospective, single-center observational study of treatment outcomes in patients with CHC and related morbidities. As such, there is no control, randomization, scheduled

intervention or prescribed dosing regimen. The medication dosing and treatment duration were at the discretion of physicians in accordance with either standard of care or local clinical practice. Data of subjects who were newly diagnosed with CHC during the year 1989 to 2011 and eligible as per inclusion/exclusion criteria were collected from the existing medical records from diagnosis date of the particular health state to the last follow-up.

Results

From 1989-2011, 54 cases were diagnosed as chronic hepatitis C. However, 49 patients had sufficient data to be enrolled into the study.

The characteristics of the study population are shown in Table 1. Among patients with non-cirrhotic chronic hepatitis C and HCV-related compensated cirrhosis, the ratios of HCV RNA level, HCV genotype and serum ALT were relatively comparable. The number of patients who received pegylated interferon alfa-2b was higher than pegylated interferon alfa-2a (61.2% vs. 36.7%). Furthermore, the higher proportion of patients who received pegylated interferon alfa-2b was observed in non-cirrhotic chronic hepatitis C group (64.9% vs. 32.4%). In this study, 85.7% of patients (42 out of 49) completed treatment course. This included 35 cases in non-cirrhotic chronic hepatitis C cohort

Table 1:

Baseline characteristics

	Non-cirrhotic chronic hepatitis C (n = 37)	HCV-related compensated cirrhosis (n = 12)	Total (n = 49)	P value
HCV RNA Level				0.56
• ≤ 850,000 IU/ml	18 (48.6%)	7 (58.3%)	25 (51.0%)	
• > 850,000 IU/ml	19 (51.4%)	5 (41.7%)	24 (49.0%)	
HCV Genotype				0.67
• Genotype 1	18 (48.6%)	5 (41.7%)	23 (46.9%)	
• Genotype non-1	19 (51.4%)	7 (58.3%)	26 (53.1%)	
Serum ALT				0.23
• < 1 time	0	1 (8.3%)	1 (2.0%)	
• 1-2 times	13 (35.1%)	3 (25.0%)	16 (32.7%)	
• > 2 times	24 (64.9%)	8 (66.7%)	32 (65.3%)	
Interferon type				0.49
• Pegylated interferon alfa-2a	12 (32.4%)	6 (50.0%)	18 (36.7%)	
• Pegylated interferon alfa-2b	24 (64.9%)	6 (50.0%)	30 (61.2%)	
• Interferon alfa-2b	1 (2.7%)	0	1 (2.0%)	
Cumulative dose				0.002
• ≥ 80%	36 (97.3%)	7 (58.3%)	43 (87.8%)	
• < 80%	1 (2.7%)	5 (41.7%)	6 (12.2%)	
Complete course of treatment	35 (94.6%)	7 (58.3%)	42 (85.7%)	0.002
Reason for stop				0.61
• Adverse event	2 (5.4%)	3 (25%)	5 (10.2%)	
• No prediction of response	0	2 (16.7%)	2 (4.1%)	

and 7 cases in HCV-related compensated cirrhosis cohort. Causes of treatment suspension in the rest of the patients were adverse events (n=5, 10.2%) and no prediction of response (n=2, 4.1%). The adverse events that were found in 5 patients who received pegylated interferon were including 2 anemia, 1 anemia with leucopenia, 1 intracerebral hemorrhage and 1 acute kidney injury.

Additionally, there was a high prevalence of suboptimal ribavirin dosage used in compensated cirrhotic group. Moreover, a significant lower rate of complete course of treatment was found in this group due to higher adverse events occurred in cirrhotic group.

Among patients who received complete course of treatment, treatment outcomes by different pegylated interferons in noncirrhotic CHC and HCV-related advance fibrosis or cirrhosis are shown in Table 2. Overall, 88.4% of patients achieved end-of-treatment virological response. The result was not significantly different between cirrhotic and non-cirrhotic group. As could be seen from the table, end-of-treatment virological response was more than 90% achieved in patient who received pegylated interferon alfa-2a irrespective of cirrhotic stage. The prevalence of CHC genotype included in the study was genotype 1 around 46.6%. There was no difference in genotype allocation between two pegylated interferon groups. In this study, viral relapse was found in 8 patients (8/38, 21.05%) and most of relapse cases (6/8, 75%) were associated with advance fibrosis or compensated cirrhosis as shown in Table 4.

The complications of hepatitis C infection are shown in Table 5. Patients were assessed at the last date of follow up. Patients were divided into two groups; patients who completed treatment courses (n=35) and patients who did not (n=7). The data shows that patients who received the complete courses of treatment had significantly lower rate of disease progression to compensated cirrhosis (4.44% vs. 28.57%, $p<0.05$), and to hepatocellular carcinoma (2.74% vs. 28.57%, $p<0.01$).

Discussions

The study includes nearly 50% of genotype 1 patients, with the standard treatment with pegylated interferon and ribavirin, the results at end-of-treatment virological response was generally higher than 80%. In addition, the virological response was good even in patients with advance fibrosis or compensated cirrhosis

Table 2:

percentage of patients that achieved end-of-treatment virological treatment response after complete course of treatment

	Non-cirrhotic chronic hepatitis C (n = 35)	HCV-related compensated cirrhosis (n = 7)
Pegylated interferon alfa-2a	14/15 (93.3%)	3/3 (100 %)
Pegylated interferon alfa-2b	18/20 (90%)	3/4 (75%)
Total (% response)	91.42	85.71

Table 3:

Genotypic distribution along with type of pegylated interferon treatment groups

	Pegylated interferon alfa-2a	Pegylated interferon alfa-2b	P-value
Genotype 1	9 (52.9%)	12 (42.8 %)	0.34
Genotype non- 1	8 (47.05%)	16 (57.14%)	0.31

who received complete course of treatments. This good result of treatments may be due to the high percentage of CC allele frequency in Southeast Asia country[1]. This is aligned with the result from the study [2] which found that sustain virological response in Asian chronic hepatitis C genotype 1 and 3 were approximately 70% and 90% respectively. However, further study would be required to understand our better result in genotype1.[3] Additionally, because the limited number of HCV-compensated cirrhotic patients (7 patients) were enrolled and received full courses of treatment in this study, to confirm the good result in this group, further research should be proposed.

Although there were more patients received pegylated interferon alfa-2b than pegylated interferon alfa-2a (61.2% vs. 36.7%) and it could be seen that patients with non-cirrhotic chronic hepatitis C at baseline received pegylated interferon alfa-2b more than pegylated interferon alfa-2a (64.9% vs. 32.4%). Among patients who received full treatment courses, the efficacy in terms of End-of-Treatment Response (ETR) in pegylated interferon alfa-2a groups were more than 90% in both non-cirrhotic and cirrhotic groups.

In cirrhotic group, one-fourth of patients stopped treatments due to adverse events. Therefore, further study should explore the degree of cirrhosis by collecting baseline characteristics such as platelet count, neutrophil count and albumin level to determine the relationship between the baseline degree of cirrhosis and the risk to develop adverse event after treatment initiation.[4]

Table 4:

Genotype and Stage of liver disease in patients who had viral relapse according to different treatment choices

Patient	Type of peg-interferon	Genotype	Stage of liver disease
1	Pegylated interferon alfa-2b	3a	cirrhosis
2	Pegylated interferon alfa-2b	3a	cirrhosis
3	Pegylated interferon alfa-2b	3a	advance fibrosis
4	Pegylated interferon alfa-2a	1	mild fibrosis
5	Pegylated interferon alfa-2a	1	cirrhosis
6	Pegylated interferon alfa-2a	1	cirrhosis
7	Pegylated interferon alfa-2b	3a	cirrhosis
8	Pegylated interferon alfa-2b	1	mild fibrosis

Table 5:

Disease progression rates to compensated cirrhosis and hepatocellular carcinoma

	Complete course of treatment (n = 45)	Not complete course of treatment (n = 7)	p
Compensated cirrhosis	4.44 %	28.57 %	0.034
Hepatocellular carcinoma	2.74%	28.57 %	0.007

Regarding the relapse rate, despite some patients had completed course of treatment and achieved end-of-treatment virological response, these patients could still undergone relapse. However, it is found that relapsers mostly had advanced fibrosis cirrhotic stage at baseline which was irrespective of genotype or type of pegylated interferon therapy used. The suboptimal dose of ribavirin could also help to predict the relapse as it is observed that there was a high prevalence of sub-optimal ribavirin dosage used in compensated cirrhotic group who undergone relapse [5-7]

As it is generally known that HCV genotype 1 patients have higher risk of relapse than genotype 3 patients. From the guidelines [8,9], two genotype 1 relapsers in this study who had only mild fibrotic stage might further benefit from the combination of pegylated interferon, ribavirin and direct-acting antiviral agents. Moreover, the study shows the importance of full-course of treatment as it is found that hepatitis C patients who were unable to complete the entire treatment courses had significantly higher rates of disease progressions to compensated cirrhosis and hepatocellular carcinoma than patients who were managed to have full courses of treatment.

Conclusions

In conclusion, high treatment outcomes were found in the management of chronic hepatitis C in Vajira Hospital. However, there were some limitations persist within the nature of the retrospective descriptive study design. More number of patients especially in cirrhotic group is needed to evaluate efficacy of treatment. To summarize, this study provides useful information about treatment paradigms, treatment outcome and disease progression in the hepatitis C patients in Vajira Hospital.

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