Original Article

Treatment Outcomes and Costs of Pegylated Interferon and Ribavirin Therapy in Chronic Hepatitis C Virus Infection

Wattana Sukeepaisarnjaroen MD[1,2], Tanita Suttichaimongkol MD[1], Kittisak Sawanyawisuth MD, PhD[1,3], Udomlack Peansukwech MSc[1], Vilai Sarapanitch RN[4], Pingpan Duangrat RN[5]

[1] Department of Medicine, Khon Kaen University, Khon Kaen, Thailand
[2] Liver Disease Research Group, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
[3] Sleep Apnea Research Group, Research Center in Back, Neck and Other Joint Pain and Human Performance, and Research and Training Center for Enhancing Quality of Life of Working Age People, Khon Kaen University, Khon Kaen, Thailand
[4] Clinic of Medicine, Outpatient clinic, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
[5] Privacy Clinic, Outpatient clinic, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

Objective: Hepatitis C virus [HCV] infection is a common infection in Thailand and Asian Pacific countries. In Thailand, a regimen of pegylated interferon plus ribavirin has been accepted for HCV treatment since April 2015. Recently, some guidelines do not recommend this regimen for HCV infection. This study aimed to evaluate the efficacy and cost of treatment by this regimen.

Materials and Methods: The study was a prospective study conducted at Khon Kaen University. The inclusion criteria were adult patients' age between 18 and 65 years with chronic HCV infection, had significant fibrosis (Metavir fibrosis score ≥F2), and treated with pegylated interferon plus ribavirin for 24 or 48 weeks depending on their genotype. Treatment outcomes and costs were analyzed by evidence of sustained virological response [SVR].

Results: There were 185 patients met the study criteria. There were 18 patients (29.0%) with genotype 1, who were unable to complete the treatment. The average SVR rate was 64.3%; genotype 3 (71.8%) and genotype 1 (50.0%). The total costs for all patients were 25,215,607 baht (US$752,705). Of those, 8,090,037 baht (US$ 241,494, 35.7%) were used for non-SVR group, particularly those patients with genotype 1.

Conclusion: Pegylated interferon plus ribavirin in chronic HCV patients with significant fibrosis had variable SVR outcomes. Genotype 1 and 3 HCV had fair outcomes due to drug intolerability or low SVR rate. Approximately one-third of the total budgets were lost for the non-SVR group.

Keywords: Chronic hepatitis C, Peg-interferon, Ribavirin, Sustained virological response, Intolerability, Cost

J Med Assoc Thai 2018; 101 [Suppl. 4]: S80-S86
Full text. e-Journal: http://www.jmatonline.com

Hepatitis C virus [HCV] infection has been reported in over 185 million people worldwide[(1)]; over 50% of infected individual live in Asia Pacific region[(2)]. Currently, treatment goal for HCV is to cure or have undetectable HCV or a sustained virological response [SVR] which is over 90% of treated patients[(3)]. If not re-infected, the SVR is sustainable for at least 5 years means cure. The SVR reduces risks of mortality, hepatic decompression, and hepatocellular carcinoma by 3.3-, 2.7-, and 1.7 fold, respectively[(4)].

In developing countries, the challenge of HCV treatment is necessary to balance between efficacy and costs of treatment. In 2016, after direct acting antiviral [DAA] implemented the European Association

Correspondence to:
Suttichaimongkol T, Division of Gastroenterology, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.
Phone: +66-43-363664, Fax: +66-43-204432
E-mail: tanisu@kku.ac.th

How to cite this article: Sukeepaisarnjaroen W, Suttichaimongkol T, Sawanyawisuth K, Peansukwech U, Sarapanitch V, Duangrat P. Treatment outcomes and costs of pegylated interferon and ribavirin therapy in chronic hepatitis C virus infection. J Med Assoc Thai 2018;101;Suppl.4:S80-S86.

for the Study of the Liver [EASL] and American Association for the Study of Liver Diseases [AASLD] guidelines do not recommend any interferon therapy for HCV infection[5,6]. However, the pegylated interferon and ribavirin may be an alternative treatment particularly in genotypes 3, 5, and 6[7]. In Thailand, pegylated interferon and ribavirin has been supported by government for treatment of HCV infection with or without HIV co-infection since April 2015. It is still recommended in chronic HCV infection genotype 1, 3, and 6 by standard criteria and evidence of significant fibrosis.

This study aimed to evaluate the efficacy and cost of treatment of chronic HCV infection by this regimen.

Materials and Methods

The study was a prospective study conducted at Srinagarind Hospital, Khon Kaen University. The study period was between May 2015 and February 2017. The inclusion criteria were adult patients' age between 18 and 65 years, the Eastern Cooperative Oncology Group [ECOG] performance status 0 to 1, diagnosed chronic HCV infection genotype 1, 2, 3, or 6 with HCV RNA ≥5,000 IU/ml, no alcohol consumption of at least 6 months and significant fibrosis which were defined by one of the following fibrosis score histopathological Metavir at least F2, or liver stiffness ≥7.5 kPa by transient elastography or ≥7.1 kPa by ultrasound elastography, or ≥4.5 kPa by magnetic resonance imaging elastography or having cirrhosis (Child-Pugh score less than or equal to 6). For human immunodeficiency virus [HIV] infected patients, CD4 must more than or equal to 350 cells/mL without HIV RNA detection if received highly active antiretroviral therapy [HAART] or CD_4 of more than or equal to 500 cells/mL if no HAART. For cancer patients, the cancer must be cured and free of cancer at least 6 months.

We excluded patients if one of the following was present: previously treated with peginterferon alfa (2a/2b) and ribavirin, history of allergy to interferon or ribavirin, uncontrolled major depression, pregnancy, plan to be pregnant, transplant patients, uncontrolled medical illnesses such as hypertension, diabetes, coronary artery disease, chronic obstructive airway disease, or hyperthyroidism, chronic alcoholism, on chemotherapy, or on addictive substance.

All eligible patients received peginterferon alfa (2a/2b) and ribavirin. The duration of treatment was based on the HCV genotypes as follows: genotype 2 and 3 for 24 weeks, genotype 1 and 6 for 48 weeks, and HIV-HCV for 48 weeks. There were 2 types of peginterferon alfa (2a/2b) available in the hospital. The HCV RNA was scheduled monitored after treatment based on HCV genotypes; genotype 2 and 3 at 24 weeks, end-of treatment response [ETR] and after ETR 24 weeks (SVR), genotype 1 and 6 at week 12 (early virological response, EVR), week 24 (if HCV was detected at week 12), ETR (at 48 weeks of treatment), and SVR (24 weeks after ETR), and HIV-HCV used same monitoring scheduled as genotype 1 and 6.

The primary outcome was the SVR of all genotypes defined by undetectable of HCV RNA at 24 weeks after ETR. There were 2 groups of patients; SVR and non-SVR group. Those with unable to tolerate the treatment or lost to follow-up were categorized as non-SVR group. Costs of treatment were calculated based on SVR and genotypes. Cost refers to the actual cost for each visit, which includes direct medical costs (medication, investigations, and management of complications) in Thai baht and US dollar. Approximate proportions of SVR in each genotype were applied to general population; the northeastern Thailand to estimate overall costs. Clinical factors and costs between those patients with or without SVR were compared by descriptive statistics. Univariate analysis was applied to calculate the crude odds ratios [OR] of individual variables associated with SVR. All significant variables or a *p*-value less than 0.20 by univariate analysis were included in multiple logistic regression analyses to calculate the adjusted odds ratios. The variance inflation factor [VIF] was calculated to assess collinearity between factors. Hosmer-Lemeshow test was use to assess goodness of fit of the model. All analyses were executed by STATA software (College Station, Texas, USA).

Results

During the study period, there were 185 patients infected with chronic HCV infection, including genotype 1 (62 patients; 33.5%), genotype 3 (85 patients; 45.9%) or genotype 6 (38 patients; 20.5%) met the study criteria. There were 18 (29.0%), 1 (1.2%), and 4 (10.5%) patients with genotype 1, 3, and 6 who were unable to complete the treatment. Baseline characteristics and laboratory results of patients categorized by SVR were comparable, as shown in Table 1.

There were 119 patients (64.3%), who had SVR. The highest SVR rate in each genotype was found in genotype 3 (71.8%) followed by genotype 6 (71.0%)

Table 1. Baseline characteristics and laboratory results of patients with hepatitis C virus infection treated with peginterferon alfa (2a/2b) and ribavirin categorized by sustained virological response (SVR) after complete treatment

Variables	Non-SVR (n = 66)	SVR (n = 119)	*p*-value
Age (years)	51 (44 to 56)	50 (45 to 55)	0.65
Male	47 (71.2)	89 (74.8)	0.59
Body mass index (kg/m^2)	24.7 (22.0 to 26.9)	23.7 (21.9 to 26.5)	0.40
Alcohol consumption	46 (69.7)	86 (72.3)	0.71
Risk factor for HCV infection			
Tattoo	14 (21.2)	30 (25.2)	0.54
Intravenous drug users	18 (28.8)	48 (40.3)	0.11
Herb use	10 (15.2)	8 (6.7)	0.07
Unsafe sex	10 (15.2)	17 (14.3)	0.87
Family history of HCV	3 (4.6)	4 (3.4)	0.68
Cirrhosis*	24 (36.9)	24 (20.3)	0.01
Peginterferon alfa			0.67
2a	23 (34.9)	38 (31.9)	
2b	43 (65.2)	81 (68.1)	
Total dose ≥80%**	20 (30.30)	62 (52.10)	0.004
Hemoglobin (g/dL)	13.8 (12.4 to 14.8)	13.9 (12.6 to 14.9)	0.54
White blood cells (cell/mm^3)	6,550 (5,300 to 7,500)	6,900 (5,800 to 8,100)	0.13
Neutrophils (%)	49.35 (44 to 56)	46.7 (41.2 to 54.5)	0.08
Absolute neutrophils count (cell/mm^3)	3,079.65 (2,508.08 to 3,754.8)	3,146 (2,350 to 4,124)	0.81
Platelet count (/mm^3)	145,000 (103,000 to 209,000)	156,000 (125,000 to 209,000)	0.25
ALT (U/L)	75.5 (48 to 104)	63 (43 to 108)	0.32
Transient elastography score (kPa)	10.8 (15.8 to 26.3)	11.8 (8.7 to 21.3)	0.07
Fibrosis score***			0.33
F2	18 (27.3)	45 (36.8)	
F3	13 (19.7)	22 (18.5)	
F4	35 (53.0)	52 (43.7)	
Genotypes of HCV			0.01
1	31 (50.0)	31 (50.0)	
3	24 (28.2)	61 (71.8)	
6	11 (29.0)	27 (71.0)	
Viral load (log IU/ml)	6.34 (6.02 to 6.63)	6.07 (5.19 to 6.5)	0.005

ALT = alanine aminotransferase; HCV = hepatitis C virus; SVR = sustained virological response
Data are presented as median (interquartile range) or number (%)
* Cirrhosis was diagnosed by ultrasonography, ** Patients received at least 80% of total peginterferon alfa (2a/2b) and ribavirin, *** Liver fibrosis scores were defined by transient elastography

and 1 (50.0%) (Table 1). Multiple logistic regression were showed four factors associated with SVR including diagnosis of cirrhosis, patients received at least 80% of total peginterferon alfa (2a/2b) and ribavirin, genotype 6 of HCV, and baseline HCV viral load with adjusted OR 2.77 (95% CI 1.32 to 5.81), 3.22 (95% CI 1.14 to 9.10), 2.92 (95% CI 1.16 to 7.33), and 0.47 (95% CI 0.30 to 0.75), respectively (Table 2). The VIF was 1.18 which it means no collinearity between factors. Hosmer-Lemeshow test was showed goodness of fit of the model, *p*-value = 0.67. Dose reduction was the strongest factor that associated with non-SVR. The main reason for reducing the dose was due to hematologic side effect including anemia, neutropenia and thrombocytopenia.

Among the 3 genotypes of HCV, the genotype 1 had the highest non-SVR including those with intolerability (50.0%). Among non-SVR group, genotype 1 had the highest cost (US$ 121,555, 70,875 and 49,063 in genotype 1, genotype 3 and genotype 6, respectively), as shown in Table 3. The treatment costs for SVR group accounted for 64.3%. The genotype 6 had highest average cost in both SVR and non-SVR groups.

When we applied the cost of treatment classified by genotype and SVR (Table 3) to all HCVtreated patients whom resisted in National health security office [NHSO] database, Thailand, of case treatment during 2 years for 4,193 patients, the costs of each subgroup were shown in Table 4. The total cost was US$ 17,060,902, which could provide seroconversion for 2,697 patients (64.3%). Approximately one-third of the total budgets were lost for the non-seroconversion group.

Discussion

The genotype distribution of HCV infection is different among continents. Genotype 1 is the most prevalent in the US (60% to 75%), while genotype 3 was more common in South and Southeast Asia, particularly Thailand[1,2]. The prevalent rates of genotype 3 HCV among these countries vary from 45% to 79%[2]. In the present study, genotype 3 was still the most common genotype (45.9%), whereas the overall SVR rate by the combination of pegylated interferon and ribavirin was 64.3%. As previously reported, genotypes, baseline viral load, and cirrhosis were factors associated with SVR[8,9]. The SVR rates in all genotypes of HCV in this study were lower than previous reports[10-12]. For example, the SVR in genotype 3 was approximately 83.7% with peginterferon with ribavirin[11], whereas the SVR rate in genotype 3 of the present study was only 71.8%. These findings may be explained by the selection criteria of study population. In the present study, all patients had at least one evidence of significant fibrosis which may lead to poorer responses to treatment. Only 18% of patients in the previous study had liver fibrosis over stage 3 (>F3)[12], whereas as 47% of our patients had >F3. Additionally, the proportion of patients who received at least 80% of total peginterferon alfa (2a/2b) and ribavirin in SVR group was significant higher than non-SVR group (adjusted OR 3.22). These findings might suggest that dose reduction was the main factor affecting the SVR rate.

Several studies showed that peginterferon plus ribavirin was a cost-effective HCV treatment[14-16]. The total costs of peginterferon plus ribavirin treatment was negative -819,921 baht and had more quality-adjusted life years by 13.1 compared with a palliative care group[14]. However, these studies had limitations since they conducted using Markov model, not a pragmatic study. It is well known that economic analysis should be interpreted carefully within the context of parameters used in the study. In this study, cost-effective model was not built but the data was collected from a real practice. The disadvantages of the peginterferon plus ribavirin treatment were that almost one-third of treatment costs were lost due to non-SVR. In other words, the SVR rate was quite lower than the new oral agents for HCV such as sofosbuvir-ledipasvir regimen in type 1 with 95% SVR[17,18]. Therefore, the guideline AASLD-IDSA recommended using non-interferon, non-ribavirin, and oral regimen for HCV infection due to high efficacy[19]. Comparing with interferon therapy, treatment with sofosbuvir and ledipasvir may save $16 billion[20].

There are some limitations in this study. This

Table 2. Univariate analysisand multiple logistic regression of factors associated with sustained virological response [SVR] after complete treatment in patients with hepatitis C virus infection treated with peginterferon alfa (2a/2b) and ribavirin

	Univariable analysis		Multiple logistic regression	
	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Cirrhosis*	2.29 (1.16 to 4.49)	0.016	2.77 (1.32 to 5.81)	0.007
Total dose ≥80%**	2.50 (1.32 to 4.72)	0.005	3.22 (1.14 to 9.10)	0.027
Genotypes of HCV***				
3	2.54 (1.27 to 5.04)		1.01 (0.34 to 2.88)	0.997
6	2.45 (1.03 to 5.79)	0.0080.040	2.92 (1.16 to 7.33)	0.022
Viral load (log)	0.55 (0.36 to 0.83)	0.005	0.47 (0.30 to 0.75)	0.009

CI = confidence interval; HCV = hepatitis C virus; OR = odds ratio; SVR = sustained virological response
* Cirrhosis was diagnosed by ultrasonography, ** Patients received at least 80% of total peginterferon alfa (2a/2b) and ribavirin, *** HCV genotype 3 and 6 compared with genotype 1

Table 3. Costs of treatment (baht) for hepatitis C virus by peginterferon alfa (2a/2b) and ribavirin according to genotypes of hepatitis C virus and treatment response as sustained virological response (SVR).

Genotype/treatment response	Baht [Non-SVR %]	Baht [SVR %]	Baht, total
Genotype 1 (n = 62)	4,072,097 (US$ 121,555)/31[50.00] x = 131,358 (US$ 3,921)	5,656,370 (US$ 168,847)/31[50.00] x = 182,464 (US$ 5,447)	9,728,467 (US$ 290,402) x = 156,910 (US$ 4.684)
Genotype 3 (n = 85)	2,374,320 (US$ 70,875)/24[28.24] x = 98,930 (US$ 2,953)	6,327,510(US$ 188,881)/61[71.76] x = 103,730(US$ 3,096)	8,701,830 (US$ 259,756) x = 102,374 (US$ 3,056)
Genotype 6 (n = 38)	1,643,620 (US$ 49,063)/11[28.95] x = 149,420 (US$ 4,460)	5,141,690 (US$ 153,483)/27[71.05] x = 190,433 (US$ 5,685)	6,785,310 (US$ 202,546) x = 178,560 (US$ 5,330)
Total (n = 185)	8,090,037 (US$ 241,494)/66[35.68] x = 122,576 (US$ 3,659)	17,125,570 (US$ 511,211)/119[64.32] x = 143,912 (US$ 4,296)	25,215,607 (US$752,705) x = 136,300 (US$ 4,069)

Data in square bracket indicated proportions of patients by genotype of hepatitis C virus or by total; Exchange rate 33.5 baht per US$

Table 4. Costs of treatment (baht) for hepatitis C virus by peginterferon alfa (2a/2b) and ribavirin according to genotypes of hepatitis C virus and treatment response for the entire patients of hepatitis C virus registries from National health security office(NHSO), Thailand (n = 4,193) using the same proportions of this study

Genotype/treatment response	Baht [Non-SVR %]	Baht [SVR %]	Baht, total
Genotype 1 (n = 1,406)	92,344,674/703 [50.00](US$ 2,756,557)	128,272,192/703 [50.00](US$ 3,829,021)	220,616,866(US$ 6,585,578)
Genotype 3 (n = 1,926)	53,817,920/544 [28.24](US$ 1,606,505)	143,354,860/1,382 [71.76](US$ 4,279,250)	197,172,780(US$ 5,885,755)
Genotype 6 (n = 861)	37,205,580/249 [28.95](US$ 1,220,614)	116,544,996/612 [71.05](US$ 3,478,955)	153,750,576(US$ 4,589,569)
Total (n = 4,193)	183,368,174/1,496 [35.68](US$ 5,473,677)	388,172,048/2,697 [64.32](US$ 11,587,225)	571,540,222(US$ 17,060,902)

SVR, sustained virological response
Data in square bracket indicates proportions of patients by genotype of hepatitis C virus or by total
Exchange rate 33.5 baht per US$

was a single site study conducted at the university hospital. The results may not apply for all levels of hospitals in Thailand. Additionally, costs were calculated only direct medical costs and indirect medical costs such as transportation, food, and accommodation or quality of life were not included.

Conclusion

Pegylated interferon plus ribavirin in chronic HCV patients with significant fibrosis had variable SVR outcomes. Genotype 1 and 3 HCV may have fair outcomes due to drug intolerability or low SVR rate.

What is already known on this topic?

In Thailand, pegylated interferon and ribavirin has been accepted for HCV with or without HIV co-infection since April 2015.

What this study adds?

Pegylated interferon-ribavirin may not be appropriate for hepatitis C virus with significant fibrosis due to variable treatment responses and treatment intolerability, particularly genotype 1.

Potential conflicts of interest

None.

References

1. Kohli A, Shaffer A, Sherman A, Kottilil S. Treatment of hepatitis C: a systematic review. JAMA 2014; 312: 631-40.
2. Lim SG, Aghemo A, Chen PJ, Dan YY, Gane E, Gani R, et al. Management of hepatitis C virus infection in the Asia-Pacific region: an update. Lancet Gastroenterol Hepatol 2017; 2: 52-62.
3. Simmons B, Saleem J, Hill A, Riley RD, Cooke GS. Risk of late relapse or reinfection with hepatitis C virus after achieving a sustained virological response: A systematic review and meta-analysis. Clin Infect Dis 2016; 62: 683-94.
4. Ng V, Saab S. Effects of a sustained virologic response on outcomes of patients with chronic hepatitis C. Clin Gastroenterol Hepatol 2011; 9: 923-30.
5. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol 2017; 66: 153-94.
6. AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. When and in whom to initiate HCV therapy [Internet]. 2016 [cited 2016 Jul 22]. Available from: https://www.hcvguidelines.org/evaluate/when-whom.
7. World Health Organization.Guidelines for the screening care and treatment of persons with chronic hepatitis C infection: updated version. Geneva: WHO; 2016.
8. Naing C, Sitt T, Aung AT, Aung K. Sustained Virologic Response to a Dual Peginterferon alfa-2a and Ribavirin in Treating Chronic hepatitis C Infection: A Retrospective Cohort Study. Medicine (Baltimore) 2015; 94: e1234.
9. Zhang GL, Chen YM, Zhang T, Cai QX, Zhang XH, Zhao ZX, et al. Favorable Outcomes of Chinese HCV-Related Cirrhotic Patients with Sustained Virological Response after Pegylated Interferon Plus Ribavirin Treatment. Biomed Res Int 2017; 2017: 8061091.
10. McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med 2009; 361: 580-93.
11. Ampuero J, Romero-Gomez M, Reddy KR. Review article: HCV genotype 3 - the new treatment challenge. Aliment PharmacolTher 2014; 39: 686-98.
12. Mangia A, Santoro R, Minerva N, Ricci GL, Carretta V, Persico M, et al. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. N Engl J Med 2005; 352: 2609-17.
13. Cheinquer H, Sette-Jr H, Wolff FH, de Araujo A, Coelho-Borges S, Soares SRP, et al. Treatment of Chronic HCV Infection with the New Direct Acting Antivirals (DAA): First Report of a Real World Experience in Southern Brazil. Ann Hepatol 2017; 16: 727-33.
14. Kapol N, Lochid-Amnuay S, Teerawattananon Y. Economic evaluation of pegylated interferon plus ribavirin for treatment of chronic hepatitis C in Thailand: genotype 1 and 6. BMC Gastroenterol 2016; 16: 91.
15. Gheorghe L, Baculea S. Cost-effectiveness of peginterferon alpha-2a and peginterferon alpha-2b combination regimens in genotype-1 naive patients with chronic hepatitis C. Hepatogastroenterology 2010; 57: 939-44.
16. Gerkens S, Nechelput M, Annemans L, Peraux B, Mouchart M, Beguin C, et al. A health economic model to assess the cost-effectiveness of PEG IFN alpha-2a and ribavirin in patients with mild chronic hepatitis C. J Viral Hepat 2007; 14: 523-36.

17. Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Subramanian GM, et al. Efficacy of nucleotide polymerase inhibitor sofosbuvir plus the NS5A inhibitor ledipasvir or the NS5B non-nucleoside inhibitor GS-9669 against HCV genotype 1 infection. Gastroenterology 2014; 146: 736-43.
18. Lawitz E, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. Lancet 2014; 383: 515-23.
19. AASLD/IDSA HCV Guidance Panel.Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology 2015; 62: 932-54.
20. Chhatwal J, Kanwal F, Roberts MS, Dunn MA. Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. Ann Intern Med 2015; 162: 397-406.