Hepatitis C Virus Treatment in the 'Real-World': How Well Do 'Real' Patients Respond?

N. Deborah Friedman^{*,†}, Joanne H. Green[§], Hanna M. Weber[§], Shiny Stephen[§], Stephen E. Lane^{†,§}, Alvin Y. Ting[‡], Jonathan P. Watson^{†,‡,§}

^{*}Department of Infectious Diseases, [†]Department of Medicine, [‡]Department of Gastroenterology, Barwon Health, and [§]Deakin University School of Medicine, Geelong, Victoria, Australia

Background: Published clinical trials of the treatment of HCV are largely multicentre prospective pharmaceutical trials. Patients in clinical trials tend to have more favorable outcomes than patients in the 'real-world', due to strict patient selection and differences in treatment conditions and available resources. **Objectives:** To assess the outcomes of Hepatitis C infected patients treated at the Barwon Health Liver Clinic with combination Pegylated interferon (PEG-IFN) and Ribavirin (RBV) therapy and to determine factors associated with a treatment response. **Methods:** Retrospective review of patients who received treatment for Hepatitis C at our institution's Liver Clinic from January 2001–September 2011. Patient demographics, comorbidities, treatment-related parameters and side effects were extracted from medical records and analyzed. **Results:** A total of 190 patients (120 male, 70 female) with a mean age of 42.8 years (range 20–68 years) commenced treatment. The most common genotype was genotype 3 (48.9%), followed by genotype 1 (42.6%). 150 of 190 patients (78.9%) completed treatment and had end of treatment data available. 107 of 182 patients, (58.8%) for whom sustained virologic response (SVR) rate data was available achieved an SVR. Overall response rates were; 46.9%, 68.8% and 62.4% in genotypes 1, 2 and 3 respectively. The response rate was significantly lower in 29 patients with documented cirrhosis (20.7%). Age, diabetes and alcohol abuse did not predict treatment response in our cohort. Side effects reported in 81.6% of patients included general malaise, hematological disturbance and psychiatric issues, and necessitated cessation of therapy in 16 patients (8.4%) and dose reduction in 26 patients (13.7%). **Conclusions:** Response rates to combination PEG-IFN and RBV therapy at our institution are comparable to other 'real-world' and pharmaceutical registration trials. Side effects of combination therapy were prominent but resulted in fewer discontinuations of therapy compared to pharmaceutical trials. (J CLIN EXP HEPATOL 2014;4:214–220)

Chronic Hepatitis C virus (HCV) infection affects an estimated 226,700 Australians, with an annual incidence of 442 new cases per annum.¹ It is a leading cause of cirrhosis and liver cancer and places a \$252 million annual burden on the health budget related to treatment costs, hospital care and lost productivity.² Furthermore, HCV causes a significant reduction in patient quality of life and wellbeing.³

Treatment for HCV aims to achieve a cure from disease as defined by a sustained virological response (SVR), and

has evolved and improved in efficacy since its introduction in the early 1990s. At the Barwon Health Liver Clinic, approximately 30–40 patients with HCV infection are treated annually with current best practice evidence-based treatment. Until recently, standard therapy has been a combination of subcutaneous PEG-IFN and oral RBV, dosed by genotype and body weight. There are however many limitations of this treatment regimen; predominantly, duration of therapy required and drug toxicity.⁴ Newer agents such as BoceprevirTM, TelaprevirTM, Sofosbuvir, Simeprevir, and Daclatasvir are altering treatment practices.^{5,6}

Current literature reveals that treatment success with PEG-IFN and RBV, ranges widely and depends on multiple factors including genotype, IL28B genotype polymorphism, baseline viral load, degree of liver damage, age, gender and ethnicity.⁷ Published clinical trials of the treatment of HCV tend to have more favorable outcomes and are largely multicenter prospective pharmaceutical registration trials, which assess treatment response in treatment-naïve patients with strict exclusion criteria and differences in treatment conditions.^{8–12} To date, there have only been 2 single-centered retrospective audits of

Keywords: hepatitis C, peginterferon alfa-2a, peginterferon alfa-2b, ribavirin

Received: 21.1.2014; Accepted: 5.7.2014; Available online: 25.7.2014

Address for correspondence: N. Deborah Friedman, Infectious Diseases Physician, Principal Research Fellow, Barwon Health, PO Box 281, Geelong VIC 3220. Tel.: +61 (0) 3 42152033

E-mail: Deborahf@barwonhealth.org.au

Abbreviations: HCV: hepatitis C virus; PEG-IFN: pegylated interferon; RBV: ribavirin; SVR: sustained virologic response; IVDU: intravenous drug use; RNA: ribonucleic acid; NSW: new South Wales; ETR: end of treatment response; PCR: polymerase chain reaction; DAAs: directly acting agents

<http://dx.doi.org/10.1016/j.jceh.2014.07.003>

HCV treatment in Australia,^{13,14} and one multi-centre study,¹⁵ of 'real-world' patients treated in normal clinical practice. Often single hospitals have limited nursing and medical resources compared to large multinational clinical trials, which may affect patient retention in HCV therapy.

The primary objective of our study was to review our centre's performance using standard of care HCV treatment and secondly to determine whether factors associated with SVR in other studies were applicable to our cohort of patients.

METHODS

We conducted a retrospective review of Barwon Health Liver Clinic patients who underwent HCV treatment from establishment of the clinic in January 2001, through to September 2011. Barwon Health is a 406-bed tertiary care teaching hospital located in Geelong, Victoria, Australia. All patients who attend the Liver Clinic at Barwon Health are managed by a multidisciplinary team comprising gastroenterologists, infectious disease physicians, a general practitioner with forensic experience, trained hepatology nurses and a dedicated clinic psychiatrist. Prior to commencing treatment, patients were required to have minimal alcohol intake, have ceased intravenous drug use (IVDU) and not be pregnant or planning a pregnancy. The clinic's psychiatrist also reviewed patients if their psychiatric state was of concern.

HCV genotyping was performed prior to treatment using a genotype assay (Versant HCV Genotype 2.0 Assay (LiPA), Bayer Health Care, Belgium). HCV RNA testing was performed at baseline, week 4, week 12, on completion of treatment and 6 months after treatment cessation using an in vitro reverse transcription-polymerase chain reaction assay (Abbott RealTime HCV Assay, Abbott Molecular, United States). Due to an evolution in the analysis of viral kinetics in HCV treatment, not all patients had HCV RNA testing performed at weeks 4 and 12, particularly early in the previous decade.

Treatment Regimens

Subsidized treatment funded by the Australian Government was made available to patients under the Section 100 guidelines (highly specialized drugs program), with eligibility criteria including age >18-year-old, contraceptive use and compensated liver disease.¹⁶

Treatment regimens for the majority of patients were a combination of weekly subcutaneous 180 mcg PEG-IFN alfa-2a and daily oral RBV (Pegasys RBV, Roche, NSW), with HCV genotype 1 patients receiving 48 weeks of therapy, and genotype 2 and 3 patients receiving 24 weeks of therapy. Dosing of RBV was 800 mg daily for genotypes 2 & 3 with weight-based dosing applied to genotype 1 patients of 1000 mg daily for those under 75 kg and 1200 mg daily

for those over 75 kg. A minority of patients received weekly subcutaneous PEG-IFN alfa-2b dosed at 1.5 mcg/kg with daily oral RBV dosed as previously described (Pegatron Combination Therapy, Merck Sharp & Dohme, NSW).

During treatment, patients were reviewed on commencement of treatment, fortnightly for the first month, and then monthly for the remaining duration of treatment, with additional review as required.

Data Collection

Patients' medical records were accessed and data extracted and entered into a study database. Patients were excluded if their medical records were incomplete.

Data regarding demographic parameters, HCV genotype and viral load, mode of acquisition, coexistent medical comorbidities and alcohol history were extracted. Where available, histological results as scored by the METAVIR system,^{17,18} and radiological results were also collected. Data regarding duration of therapy, side effects experienced, dose reductions and treatment responses were recorded. Treatment efficacy was described according to; non-response, early, end of treatment (ETR) and sustained virologic responses (SVR), and relapse after therapy.¹⁹

Statistical Analysis

Descriptive statistics were presented as numbers and percentages. The association between increasing age (measured in quintiles) and SVR was determined using Fisher's exact test. Logistic regression was used to determine the associations between; genotype, age, cirrhosis, diabetes, alcohol abuse and IVDU mode of acquisition with SVR. Two models were tested, the first using age as a continuous variable and the other using age as a categorical variable.

Ethics Approval

This research study was approved by the Human Research Ethics Committee at Barwon Health, Geelong, Australia.

RESULTS

Two hundred and eight patients either received or were planned to receive the PEG-IFN and RBV treatment (Figure 1). Of these, 18 patients were excluded due to failure to commence the prescribed therapy or incomplete medical records. The remaining cohort of 190 patients was analyzed. Each patient was only included once, with re-treated patients being included only in their most recent treatment episode.

Patient Characteristics

Patient characteristics of the final cohort ($n = 190$) are shown in Table 1. The mean age of the treatment cohort

a = 4 patients who ceased therapy due to side effects had end of treatment data available

Figure 1 Flow chart of patients attending Barwon Health Liver Clinic (January 2001–September 2011).

was 42.8 years, and males accounted for 63.2% of the cohort. Genotype 3 was most common (93/190, 48.9%), and the predominant mode of acquisition was intravenous drug use (140/190, 73.7%). Of the 177 patients for whom data was available regarding hepatic cirrhosis, 29 patients (16.4%) had clinical, radiological or histological evidence of cirrhosis.

Virological Responses and Predictors

ETR data was available in 150 of 190 patients (78.9%) who commenced therapy. Forty patients were either lost to follow-up (10), early non-responders (14), or ceased treatment early due to side effects (16). Four patients completed treatment but had no end of treatment data available, and 4 patients who ceased treatment early due to side effects had end of treatment data available (Figure 1).

Evaluation of end of treatment data revealed that 139 of 150 patients (92.7%) who completed therapy (or 139 of 190 patients who commenced therapy, 73.2%) had an end of treatment response and were PCR negative at the completion of treatment, while 11 patients were non-responders at the completion of treatment (Figure 1). Of those 139 patients who had an ETR, 24 patients relapsed within 6

months of completion of treatment and no SVR data was available for 8 patients. The remaining 107 patients of 182 patients (for whom SVR data was available) achieved an SVR (58.8%).

Analysis by genotype revealed SVR rates of 46.9% in genotype 1, 68.8% in genotype 2 and 62.4% in genotype 3. Analysis of SVR and possible associated factors revealed that cirrhosis significantly decreased the odds ratio (OR) of SVR (OR 0.16, 95% confidence interval (CI): 0.05, 0.45). There was no significant relationship between diabetes, alcohol abuse or IVDU mode of acquisition and SVR in our cohort ((OR 0.84, 95% CI: 0.20, 4.38), (OR 1.72, 95% CI: 0.83, 3.72), (OR 1.58, 95% CI: 0.74, 3.34) respectively). Increasing age was not found to have an effect on SVR rates (OR 0.98, 95% CI: 0.94, 1.02).

Twenty-five of 182 patients for whom SVR data was available (13.7%) were non-responders to treatment. Fourteen patients were early non-responders with no significant drop in viral load at 12 weeks. Of these early non-responders, 12 were genotype 1, and 2 were genotype 3. A further 11 patients failed to have an ETR (8 were genotype 1 and 3 were genotype 2).

Table 1 Selected Baseline Demographic Data of Cohort (n = 190).

Characteristic	n (%)
Gender	
Male	120 (63.2)
Female	70 (36.8)
Mean age at time of treatment	42.8 years
Median age at time of treatment	44.5 years (20–68)
Caucasian	177 (93.2)
HCV genotype	
1	81 (42.6)
2	16 (8.4)
3	93 (48.9)
Cirrhosis	29 (16.4)
Mode of acquisition ^a	
IVDU	140 (73.7)
Tattoos/piercings	34 (17.9)
Transfusion	20 (10.5)
Household	20 (10.5)
Unknown	31 (16.3)
Previous alcohol abuse	81 (42.6)
Diabetes	11 (5.8)
HIV positive	5 (2.6)
HBsAg positive	12 (6.3)

^aIn 43 patients there was >1 suspected mode of acquisition of HCV.

Side Effects and Treatment Cessation

Side effects to therapy were reported in 81.6% of 190 patients. The most common side effects experienced included general malaise (46.3%), hematological disturbances (42.1%) and psychiatric issues (36.8%). Other side effects encountered by patients in the study can be seen in Figure 2. Forty of the 190 patients (21.1%), all male, did not complete their planned treatment course; 16 ceased treatment early because of side effects. Age was not associated with development of side effects. Twenty-six patients (13.7%) had their treatment dose reduced, predominantly due to hematological side effects according to manufacturer recommendations.²⁰ Both increasing age (OR 1.09, 95% CI: 1.03, 1.16) and female gender (OR 2.78, 95% CI: 1.03, 7.85) were associated with dose reduction.

DISCUSSION

Numerous community-based trials have shown that treatment of HCV infected patients with PEG-IFN and RBV, under 'real-world' conditions is associated with results that are comparable to clinical trials.^{11–13,21–25} In this 10 year retrospective study, 107 patients of 182 patients for

Figure 2 Side effects of pegylated interferon and ribavirin therapy.

whom SVR data was available (58.8%) achieved an SVR. Patients with genotype 1 had the lowest SVR (46.9%), compared to genotypes 2 and 3 (68.8% and 62.4% respectively). These results remain in the range of other 'real-world' trials that have been conducted both nationally and internationally (Table 2). Our results for genotype 1 are similar to those reported in registration clinical trials, however, SVR for genotypes 2 and 3 were lower than those demonstrated in pharmaceutical trials.^{8–11} Previous multi-centre, open-label community trials in the United States and Canada had much lower outcomes across all genotypes, when compared to the drug registration trials.^{26,27} These lower results have been suggested to be due to the large number of patients included in the analysis who were lost to follow-up.²¹ Similarly, in the present study, loss of patients to follow-up occurred before treatment commenced, after treatment commenced and after the end of treatment (Figure 1).

Our study found that patients with cirrhosis had significantly lower SVR rates (20.7%), which is in keeping with the findings of other studies, showing a significant step-wise decline in SVR with increasing fibrosis stage.²⁸ This highlights the importance of early HCV treatment, preempting the development of significant cirrhosis. While diabetes has been shown to decrease overall SVR rates, this was not shown to be statistically significant in our study. This is supported by the literature, which reveals mixed results regarding the extent to which diabetes is suggested to impact upon SVR outcomes.^{29,30} While the literature suggests that age (especially over 65 years), is associated with lower rates of SVR and higher rates of relapse,³¹ data for IVDU mode of acquisition,^{32,33} and past alcohol abuse,³⁴ have not been shown to correlate as strongly. In our study neither age, IVDU mode of acquisition nor past alcohol abuse were found to be significant predictors of a poor SVR result in our study. These are encouraging findings, suggesting that patients with a history of IVDU and alcohol abuse can be successfully treated, although they may have been excluded from HCV treatment in the past.³⁵

Barriers to HCV treatment do exist in the 'real-world'. The majority of HCV infected patients are unaware of their

Table 2 SVR Rates Across Pharmaceutical and 'Real-World' Trials.

Study type	Author, year, drug formulation	Genotype 1	Genotype 2 + 3		Overall
Prospective pharmaceutical registration trials	Fried et al (2002) ⁷ PegIFN alfa-2a + RBV	46%	76%		56%
	Hadziyannis et al (2004) ⁸ PegIFN alfa-2a + RBV	52%	84%		63%
	McHutchinson et al (2009) ⁹ PegIFN alfa-2b + RBV, PEG-IFN alfa-2a + RBV	28%	66%		39.8% (standard dose alfa-2b), 38% (low dose alfa-2b), 40.9% (alfa-2a)
	Manns et al (2001) ¹⁰ PegIFN alfa-2b + RBV	42% (higher dose pegIFN), 34% (lower dose)	80%	80%	54%, 47%
Australian 'real-world' trials	Our cohort PegIFN alfa + RBV	46.9%	68.8%	62.4%	56.3%
	Gidding et al (2012) ¹³ PegIFN alfa + RBV	49.5%	69.6%		59.5%
	Kumar et al (2003) ¹¹ IFN alfa-2b + RBV	47%	38%	71%	53%
	Muller et al (2012) ¹² PegIFN + RBV	55.2%	81.8%	72.3%	–
International 'real-world' trials	Jacobsen et al (2007) ²³ PegIFN alfa2b + RBV	34% (weight-based RBV dose), 28.9% (flat dose)	61.8%	59.5%	44.2%, 40.5%
	Abadir et al (2005) ²⁴ PegIFN alfa2a + RBV	41.6%	79.0%	72.0%	54.3%
	Borrioni et al (2008) ¹⁹ PegIFN + RBV	46%	84%		64%
	Withoeft et al (2010) ²⁰ PegIFN alfa2a/2b + RBV	46.5%	77.3%		57.9%
	Bourliere et al (2012) ²¹ PegIFN alfa2a + RBV	42%	69%		54%
	Pariente (2010) ²² PegIFN alfa2a/2b + RBV	37.1%	70.5%	71%	50%

infection, and this coupled with both a lack of awareness about HCV and often infrequent presentation for medical care affect both diagnosis and specialist referral.³⁶ Even patients who are aware that they are infected with HCV may fear the side effects of therapy or have comorbid conditions such as psychiatric disease and active injecting drug use, which act as barriers to both specialist referral and treatment initiation.³⁶ Furthermore, non-adherence due to poor awareness, in addition to social and economic pressures may affect the ability of patients to either commence or complete therapy.³⁶ As has been found by others, in our cohort some of the excluded patients did not complete their pre-treatment evaluation, and 8 patients did not have laboratory testing done to confirm an SVR.³⁷

Our study also addressed side effects experienced from the PEG-IFN and RBV combination treatment, a factor not significantly analyzed in similar studies.^{8–10,13,21,23} While 81.6% of the treated patients in this study experienced some side effects, only 8.4% ceased treatment prematurely. These discontinuation rates are better than those reported in some registration clinical trials, which range from 14 to 21%,^{8,10,11} and are similar to other cohort studies in clinical practice.^{13,22,23} These results

suggest that the tolerability of HCV treatment can be similar, if not better, in every-day practice to that seen in highly supported clinical trials. In clinical trials and the study by Borrioni et al, over 25% of patients required a dose reduction of one or both drugs because of laboratory abnormalities or adverse clinical events.^{11,22} In contrast only 13.7% of patients in our study required a dose reduction of their medications during their planned course. While older age and male sex have been found to be the strongest predictors of treatment discontinuation or a reduction in dose previously,²² in our study, males were most likely to cease treatment, however, female gender was more strongly correlated with dose reduction.

The most common side effects experienced in our cohort were; general malaise (46.3%), hematological disturbances (42.1%) and psychiatric issues (36.8%). These findings are both consistent with those from clinical trials,^{8,10} and are in keeping with the product information for PEG-IFN and RBV combination therapy.²⁰ While newer therapies that may shorten treatment duration hold great promise for improving future treatment options, the side effect profiles of some products are similarly problematic.³⁸ There has however been a rapid

development of new drugs, including interferon-free therapy using the polymerase inhibitor Sofosbuvir with RBV.^{39–41} The new European Association for the Study of The Liver (EASL) guidelines now recommend several directly acting agents (DAAs) as standard of care in HCV infection, including; Boceprevir, Telaprevir, Sofosbuvir, Simeprevir and Daclatasvir.⁶

There are a number of limitations to our study. Firstly, it is a retrospective study, which affects the ability to interpret clinical reasoning during data extraction, especially regarding side effects and treatment cessation. Also, incomplete or inconsistently recorded data affected the completeness of many patients' data sets thus decreasing our ability to draw statistical conclusions regarding some variables. In addition, we could not determine rapid, early and sustained virologic responses in all patients because initial, early treatment and after therapy viral load assessments were not available in all cases, which would have been desirable. Finally, our patient cohort is small relative to other similar studies. However, as our study analyzes patient data over a ten-year period it is likely to be representative of a typical outpatient Western population at a regional teaching hospital. We believe that the data from our clinic captures a true 'real-world' setting.

CONCLUSION

In conclusion, our study reveals that response rates to HCV treatment among 'real-world' patients in a regional Australian hospital liver clinic are as good as those seen in pharmaceutical registration trials. Despite including patients with more varied medical and lifestyle comorbidities, as well as potentially not being able to provide the same levels of support and monitoring during treatment compared to clinical trials, these results remain comparable. These findings suggest that HCV treatment can be offered to a broader range of patients, significantly impacting on overall treatment success. As newer combination therapies emerge, the impact of triple therapy and interferon-free regimens will need to be investigated in the 'real-world' setting.

AUTHOR CONTRIBUTIONS

Study concept and design: Watson, and Friedman. Interpretation of data: Green, Ting, and Friedman. Drafting of the manuscript: Green, Weber, Stephen, and Ting. Critical revision of the manuscript for important intellectual content: Friedman, and Watson. Data analysis: Lane, Green and Ting.

CONFLICTS OF INTEREST

All authors have none to declare.

ACKNOWLEDGMENTS

We would like to thank the Liver Clinic Nurses: Susan Streat, Melissa Heath and Margaret Wardrop. We would also like to thank our colleagues at the Barwon Health liver clinic who cared for these patients during the 10 years included in this study, and Dr Lauren Beswick, and Dr John Ding, gastroenterology trainees during the course of the study data analysis.

REFERENCES

1. The Kirby Institute. *HIV, Viral Hepatitis and Sexually Transmissible Infections in Australia*. Annual Surveillance Report; 2012. Accessed at: <http://passthrough.fw-notify.net/download/055316/http://www.ashm.org.au/images/Media/ASR2013.pdf>.
2. Boston Consulting Group. *The Economic Impact of Hepatitis C in Australia* [Online, 01 February 2013]. Boston Consulting Group; 2012.
3. Department of Health and Ageing. *National Hepatitis C Resource Manual*. 2nd ed. Accessed at: <http://www.health.gov.au/internet/main/publishing.nsf/Content/phd-hepc-manual-2008>.
4. Bernstein D, Kleinman L, Barker C, Revicki D, Green J. Relationship of health related quality of life and treatment adherence and sustained response in chronic hepatitis C patients. *Hepatology*. 2002;35:704–708.
5. Hepatitis Australia. A Guide to Current and Emerging Hepatitis C Treatments. Accessed at: <http://www.hepatologyassociation.com.au/images/stories/news/Guide-to-hepatitis-C-treatments1.pdf>.
6. EASL Recommendations on Treatment of Hepatitis C; April 2014. Accessed at: http://www.easl.eu/_newsroom/latest-news/easl-recommendations-on-treatment-of-hepatitis-c-2014.
7. Kau A, Vermehren J, Sarrazin C. Treatment predictors of a sustained virological response in hepatitis B and C. *J Hepatol*. 2008;49:634–651.
8. Fried M, Shiffman M, Reddy K, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med*. 2002;347:975–982.
9. Hadziyannis S, Sette Jr H, Morgan T, et al. PEGASYS International Study Group. Peginterferon-alfa2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med*. 2004;140:346–355.
10. McHutchison J, Lawitz E, Shiffman M, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med*. 2009;361:580–593.
11. Manns M, McHutchison J, Gordon S, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet*. 2001;358:958–965.
12. Martin K, Begaud B, Latry P, Miremont-Salame G, Fourrier A, Moore N. Differences between clinical trials and postmarketing use. *Br J Clin Pharmacol*. 2004;57:86–92.
13. Kumar D, Wallington-Beddoe C, George J, et al. Effectiveness of interferon alfa-2b/ribavirin combination therapy for chronic hepatitis C in a clinic setting. *Med J Aust*. 2003;178:267–271.
14. Muller K, Rodgers A, Wundke R, et al. Single centre experience with pegylated interferon and ribavirin for hepatitis C: looking back before moving forward. *Intern Med J*. 2012;42:765–772.
15. Gidding H, Law M, Amin J, et al. Hepatitis C treatment outcomes in Australian clinics. *Med J Aust*. 2012;196:633–637.
16. Department of Health and Ageing. Section 100 – Highly Specialised Drugs Program. Accessed at: <http://www.pbs.gov.au/info/browse/section-100/s100-highly-specialised-drugs>.

17. Bedossa P, Poinard T. An algorithm for the grading of activity in chronic hepatitis C. *Hepatology*. 1996;24:289.
18. [No authors listed]. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. *Hepatology*. 1994;20:15–20.
19. Thompson AJ, Muir AJ, Sulkowski MS, et al. Interleukin-28B polymorphism improves viral kinetics and is the strongest pretreatment predictor of sustained virologic response in genotype 1 hepatitis C virus. *Gastroenterology*. 2010;139:120–129.
20. Roche. PEGASYS RBV (Peginterferon Alfa-2a and Ribavirin) Product Information. Accessed at: http://www.roche-australia.com/home/products/pharmaceuticals/pegasys_rbv.html.
21. Marotta P, Hueppe D, Zehnter E, Kwo P, Jacobson I. Efficacy of chronic hepatitis C therapy in community based trials. *Clin Gastroenterol Hepatol*. 2009;7:1028–1035.
22. Borroni G, Andreoletti M, Casiraghi M, et al. Effectiveness of pegylated interferon/ribavirin combination in 'real world' patients with chronic hepatitis C virus infection. *Aliment Pharmacol Ther*. 2008;27:790–797.
23. Witthoef T, Hueppe D, John C, et al. Efficacy and tolerability of peginterferon alfa-2a or alfa-2b plus ribavirin in the daily routine treatment of patients with chronic hepatitis C in Germany: the PRACTICE study. *J Viral Hepat*. 2010;17:459–468.
24. Bourliere M, Ouzan D, Rosenheim M, et al. Pegylated interferon- α 2a plus ribavirin for chronic hepatitis C in a real-life setting: the Hepatys French cohort (2003–2007). *Antivir Ther*. 2012;17:101–110.
25. Pariente A, Lahmek P, Duprat C, et al. Treatment of chronic hepatitis C with pegylated interferon and ribavirin in treatment-naïve patients in 'true life': a plea in favor of independent postmarketing evaluations. *Eur J Gastroenterol Hepatol*. 2010;22:1297–1302.
26. Jacobson I, Brown Jr R, Freilich B, et al. Peginterferon alfa-2b and weight-based or flat-dose ribavirin in chronic hepatitis C patients: a randomized trial. *Hepatology*. 2007;46:971–981.
27. Abadir N, Marotta P, Fenman S, et al. Pegatron prospective optimal weight-based dosing response program (POWER): preliminary results. *Hepatology*. 2005;42:693.
28. Cheng W, Roberts S, McCaughan G, et al. Low virological response and high relapse rates in hepatitis C genotype 1 patients with advanced fibrosis despite adequate therapeutic dosing. *J Hepatol*. 2010;53:616–623.
29. Brandman D, Bacchetti P, Ayala C, Maher J, Khalili M. Impact of insulin resistance on HCV treatment response and impact of HCV treatment on insulin sensitivity using direct measurements of insulin action. *Diabetes Care*. 2012;35:1090–1094.
30. Eslam M, Aparecero R, Kawaguchi T, et al. Meta-analysis: insulin resistance and sustained virological response in hepatitis C. *Aliment Pharmacol Ther*. 2011;34:297–305.
31. Yu J, Sun L, Kang P, Yan B, Zhao Y. Efficacy and factors influencing treatment with peginterferon alpha-2a and ribavirin in elderly patients with chronic hepatitis C. *Hepatobiliary Pancreat Dis Int*. 2012;11:185–192.
32. Hellard M, Sacks-Davis R, Gold J. Hepatitis C treatment for injection drug users: a review of the available evidence. *Clin Infect Dis*. 2009;49:561–573.
33. Seal K, Currie S, Shen H, et al. Hepatitis C treatment candidacy and outcomes among 4318 US veterans with chronic hepatitis C virus infection does a history of injection drug use matter? *J Clin Gastroenterol*. 2007;41:199–205.
34. Russel M, Pauly M, Moore C, et al. The impact of lifetime alcohol use on hepatitis C treatment outcomes in privately insured members of an integrated health care plan. *Hepatology*. 2012;56:1223–1230.
35. Gidding H, Law M, Amin J, et al. Predictors of deferral of treatment for hepatitis C infection in Australian clinics. *Med J Aust*. 2011;194:398–402.
36. McGowan CE, Fried MW. *Barriers to Hepatitis C Treatment*. Liver International; 2012. Accessed at: <http://www.ihepa.com/UploadFiles/PHC2012/pdf/2706.pdf>.
37. Falck-Ytter Y, Kale H, Mullen KD, et al. Surprisingly small effect of antiviral treatment in patients with hepatitis C. *Ann Intern Med*. 2002;136:288–292.
38. Pearlman B. Protease inhibitors for the treatment of chronic hepatitis C genotype-1 infection: the new standard of care. *Lancet Infect Dis*. 2012;12:717–728.
39. Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med*. 2013;368:34–44.
40. Jacobsen IM, Gordan SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med*. 2013;368:1867–1877.
41. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med*. 2013;368:1878–1887.