Gastroenterology Report, 5(3), 2017, 208–212

doi: 10.1093/gastro/gow033
Advance Access Publication Date: 24 October 2016
Original article

ORIGINAL ARTICLE

Real world experience with pegylated interferon and ribavirin in hepatitis C genotype 1 population with favourable *IL28B* polymorphism

Victoria Ekstrom[1,*], Rajneesh Kumar[1], Yi Zhao[2], Mei Ling Yee[3], Cynthia Sung[4,5], Dorothy Toh[4], Poh Yen Loh[6], Jessica Tan[6], Eng Kiong Teo[6], Wan Cheng Chow[1]

[1]Department of Gastroenterology and Hepatology, Singapore General Hospital, Singapore, [2]Department of Clinical Translational Research, Singapore General Hospital, Singapore, [3]Department of Pharmacy, Singapore General Hospital, Singapore, [4]Health Products Regulation Group, Health Sciences Authority, Singapore, [5]Emerging Infectious Disease Programme, Duke-NUS Medical School, Singapore and [6]Department of Gastroenterology and Hepatology, Changi General Hospital, Singapore

*Corresponding author. Department of Gastroenterology and Hepatology, Singapore General Hospital, Outram Road Singapore 169608, Singapore. Tel: +65-98774539; E-mail: vekstrom@gmail.com

Abstract

Background and aim: Conventional hepatitis C treatment using pegylated interferon (PEG-IFN) and ribavirin is associated with significant side effects. *IL28B* polymorphism can predict response to treatment, with CC genotype having a better response. *ITPA* gene deficiency protects against clinically significant anaemia induced by treatment. The purpose of this study was to determine *IL28B* polymorphism and *ITPA* variation among hepatitis C genotype 1 patients who have undergone therapy with PEG-IFN and ribavirin and their association with sustained viral response (SVR).
Methods: All hepatitis C genotype 1 patients who had been treated with PEG-IFN and ribavirin over the past 10 years were identified by available medical records and were contacted by letter of invitation to participate in the study. Blood samples for *IL28B* and *ITPA* genotyping were obtained. Medical records were reviewed for verification of treatment response, development of anaemia and if treatment reduction was required during the treatment.
Results: A total of 61 patients with hepatitis C genotype 1 were treated with PEG-IFN and ribavirin, of whom 42 agreed to participate in the study. Mean age was 45.6±12.9 years at time of treatment, and 83.3% of patients were males. Thirty-three (78.6%) had *IL28B* CC genotype, of whom 25 (75.8%) obtained SVR compared with only 3 of 9 (33.3%) non C/C genotype patients who achieved SVR (P=0.041). Eleven (26.1%) patients had *ITPA* AC genotype, and 30 (71.4%) had CC genotype. There was no statistically significant difference between *ITPA* AC and CC genotypes in predicting clinically significant anaemia (45.5% *vs* 63.3%, P=0.302). Even among patients who developed anaemia, 70.8% still managed to achieve SVR. Treatment reduction also had no impact on SVR.
Conclusion: Hepatitis C genotype 1 patients should be informed of the response rate for treatment with PEG-IFN and ribavirin in a population with favourable IL28B genotype before consideration of newer therapeutic options.

Submitted: 4 July 2016; **Revised:** 22 August 2016; **Accepted:** 4 September 2016

Key words: hepatitis C; pegylated interferon; IL28B polymorphism; sustained viral response

Introduction

Genotype 1 hepatitis C infection (HCV) is the most common Hepatitis C infection, accounting for 46.2% of all HCV cases, approximately one-third of which occur in East Asia. [1]. Genotype 1 infection has been historically reported as being difficult to treat [2,3] until the advent of direct-acting antiviral agents (DAAs). DAAs are well tolerated and are an oral regimen, with multiple studies reporting sustained viral response rates (SVR) > 90% in Genotype 1 patients [4,5]. However, the accessibility of these direct-acting antiviral agents has been complicated by the high price of therapy [6]. Many times, use of these new drugs is either limited by individual patient's ability to afford them in places where patients have to pay for their own medications or patients who already have significant complications from HCV infection even in countries with national healthcare schemes [7,8]. Data from Asia have shown favourable responses to pegylated interferon (PEG-IFN) and ribavirin in patients with hepatitis C and been attributed to favourable *IL28B* genotypes [9–11]. Hence, healthcare providers may still have to consider PEG-IFN in combination with ribavirin as a treatment option [12]. The patients, as well as the local health policy makers, can only make reasonable and informed decisions if they have enough knowledge about the success rates and what contributes to the success of conventional and new treatments. The decision is affected by the success rate experienced in local populations. In Singapore, which is made up of a diverse population with the ethnic distribution of 74.3% Chinese, 13.3% Malay and 9.1% Indians [13], data for SVR in patients treated with PEG-IFN and ribavirin are much needed.

It is known that certain host factors predict better response to therapy with PEG-IFN and ribavirin [11,14]. The difference in response rates between African-Americans and Caucasians is largely explained by genetic differences in the *IL28B* gene region on chromosome 19 [11,15]. The majority of African-Americans have either of the less favourable genotypes (CT or TT) [15]. The CT or TT genotype was associated with a 40% lower SVR rate compared with patients having the CC allele. The IL28B CC genotype, which is the favourable genotype, is the predominant genotype in China [16]. Singapore, which is a multi-ethnic country with a predominantly Chinese population, also demonstrates a high proportion of CC genotype [17].

In addition, the inosine triphosphate (ITPA) gene (*rs1127354* and *rs7270101)* is known to provide protection against anaemia during therapy [18]. Patients who do not develop anaemia are more likely to comply and receive the full course of therapy, which is important as SVR increases with higher levels of dose compliance of PEG-IFN and ribavirin [19,20]. The *ITPA* variation is unknown in Singapore.

It could potentially be highly cost effective to screen patients for IL28B prior to determining which therapy to prescribe, especially in resource-poor countries and places in which patients have to pay for their medications out of pocket. Therefore, in this study, we aimed to determine the *IL28B* genotype and *ITPA* variations among HCV genotype 1 patients who have undergone therapy with PEG-IFN and ribavirin and their association with SVR in order to see if we can predict the response to therapy based on these two host factors.

Patients and methods

Patients

All patients with HCV genotype 1 who were previously treated with PEG-IFN and ribavirin at the Department of Gastroenterology and Hepatology at Singapore General Hospital between 2004 and 2015 were identified by available medical records. Patients were treated with PEG-IFN alfa-2a and weight-based ribavirin for 48 weeks. The dose of PEG-IFN alfa-2a was 180 μg subcutaneously per week, and the ribavirin dose was 1000 mg/day for patients weighing <75 kg and 1200 mg/day for patients weighing>75 kg. The patients were contacted by a letter inviting them to participate in the study. Blood samples for *IL28B* and *ITPA* genotyping were obtained from the patients who agreed to participate in the study. Medical records were reviewed for verification of the duration of therapy, response to therapy, development of anaemia and if erythropoietin was required during the treatment. Prior approval from the ethical committee was obtained from the ethics review board per Helsinki guidelines for human research.

Gene tests

Peripheral venous blood was collected from all participants in EDTA-containing tubes. Genomic DNA was extracted from 400 μL of whole blood using the Maxwell 16 DNA Purification Kit (Promega) on the Maxwell MDX 16 automatic DNA extraction instrument (Promega) per the manufacturer's instructions. Finally, DNA was eluted with 400 μL elution buffer. DNA concentration was measured using Nanodrop spectrophotometer ND-1000 (Thermo Fisher Scientific). *IL28B* polymorphism (rs12979860, rs8099917) and *ITPA* variations (rs7270101, rs1127354) were tested using TaqMan® Assays (Applied Biosystems) per manufacturer's instructions. Primers used are mentioned in the manufacturer's protocol.

Definitions

SVR is defined as undetectable HCV RNA level using a sensitive assay 24 weeks after completion of therapy for hepatitis C. Anaemia was defined as either a decline in hemoglobin (Hb) of 3 g/dL or a drop of Hb levels to <10 g/dL. Treatment discontinuation was defined as patients who were unable to complete the 48-week course. Patients were defined as being cirrhotic if they met at least two out of three criteria (splenomegaly, caudate lobe hypertrophy or coarsened echotexture) on imaging or had a transient elastography reading >12.5 kPa.

Outcome measurement

The primary outcomes of the study were IL28B polymorphism and ITPA gene variation among GT1 HCV patients who underwent therapy with PEG-IFN, and ribavirin and their association with SVR. The secondary outcome was the incidence of discontinuation or interruption of treatment due to side effects.

Statistical analysis

Statistical analysis was carried out using SPSS 21.0 (Chicago, IL). Continuous variables are expressed as mean ± standard deviation (SD), while categorical variables are expressed as actual numbers and their percentages. Continuous variables were compared using analysis of variance, and categorical variables were compared using the chi-square test or Fisher exact test. A P value <0.05 was considered statistically significant.

RESULTS

Patient characteristics at initiation of treatment

There were 61 patients who had previously undergone treatment, and the SVR was 73.8% with mean age of 43.2 ± 12.0 years. Treatment discontinuation was seen in 14.8% (9/61) of patients. Out of these 61 patients, 42 (68.8%) patients agreed to participate in the study. The mean age of the study population was 45.6 ± 12.9 years at the time of treatment, and 83.3% of the patients were males. Demographic and clinical parameters of the 42 patients were presented in Table 1.

IL28B polymorphism and ethnicity

In keeping with the racial distribution in Singapore, 32/42 (76.1%) patients were Chinese, and 27/32 (84.3%) had a predominantly CC genotype (Table 2).

ITPA polymorphism, anaemia and treatment reduction

Eleven (26.1%) patients had *ITPA* AC genotype, 30 (71.4%) had CC genotype, and only one (2.3%) had AA genotype. Five (45.5%) of the patients with AC genotype developed clinically significant anaemia compared with 19 (63.3%) of the patients with CC genotype (P=0.302, Table 3). In such instances, these patients required either an attenuated dose of ribavirin or were started on erythropoietin.

The patients who developed anaemia were more likely to get a treatment reduction (11/24 *vs* 3/18, P=0.057). The median dosage of ribavirin was 800 mg/day over a course of 35 weeks in patients who had reduced dosages of ribavirin compared with 1000 mg/day over a course of 48 weeks for patients who received the full course of treatment.

Treatment response

In the 42 patients who agreed to participate in the study, SVR was seen in 28 (66.7%). Eight (19.0%) patients discontinued treatment due to the following reasons: two were lost to follow-up; two had failed early response to treatment (HCV RNA decrease <2 log) and were discontinued at week 24; four were intolerant of PEG-IFN and ribavirin; two developed symptomatic anaemia; one (2.4%) developed pancytopenia; and one perceived low mood. Six (14.3%) patients had a shortened duration of treatment due to missed dosages.

Thirty-three (78.6%) patients had IL28B C/C genotype, of whom 25 (75.8%) obtained SVR compared with only 3/9 (33.3%) non-C/C genotype patients who achieved SVR (P=0.041); however, neither anaemia nor treatment reduction was found to have an impact on SVR (Table 4).

Table 1. Patient characteristics (N = 42)

Age (years)	45.6 ±12.9
Male	35 (83.3%)
Race	
Chinese	32 (76.2%)
Malay	4 (9.5%)
Indian	2 (4.8%)
Other	4 (9.5%)
Genotype	
1a	18 (42.9%)
1b	20 (47.6%)
1 (indeterminate subtype)	4 (9.5%)
Cirrhosis	7 (20%)
Previous treatment	0 (0%)
ALT (normal range 10–55 U/L)	81.4±42.1
Hemoglobin (normal range 11.5–15.0 g/dL)	14.8±1.4
WBC (normal range 4–10 ×109/L)	5.8±1.5
Platelet (normal range 140–440 ×109/L)	201 ± 68

ALT: alanine transaminase; WBC: white blood cell

Discussion

The field of chronic hepatitis C has been revolutionised by the appearance of the newer DAAs [21–24], but their very high costs have limited their accessibility. Nonetheless, chronic hepatitis C should be treated to avoid the burden of chronic liver disease [25–27]. Health authorities in various countries have tried to rationalise their health expenditure by confining its use to patients with severe liver disease as defined by degree of fibrosis or presence of cirrhosis [28,29]. However, treatment by which time may be too late to avoid the complications associated with chronic hepatitis C despite successful treatment [30]. There could perhaps be other criteria for rationalising the use of DAAs rather than just purely the severity of liver disease.

PEG-IFN and ribavirin should still be considered a viable combination in populations with favourable IL28B genotype [31]. It is known that *IL28B* genotypes can predict response to treatment with interferon and ribavirin to hepatitis C and that *ITPA* variant, which predicts the development of anaemia in patients on interferon [15,18], can have an impact on the total

Table 2. IL28B polymorphism (rs12979860) and ethnicity

Ethnicity	Polymorphism	
	CC	CT & TT
Chinese (N = 32)	27	5
Malay (N = 4)	3	1
Indian (N = 2)	0	2
Others (N = 4)	3	1

Table 3. ITPA Polymorphism (rs1127354) and anaemia

Polymorphism	Anaemia	No anaemia
AC (N = 11)	5	6
CC (N = 30)	19	11
AA (N = 1)	0	1

Table 4. Influence of *IL28B* polymorphism, anaemia and treatment reduction on sustained viral response (SVR)

	SVR	Failed SVR	P value
IL28B polymorphism			0.041
CC (N = 33)	25 (78.6%)	8 (21.4%)	
CT & TT (N = 9)	3 (33.3%)	6 (66.7%)	
Anaemia			0.508
Yes (N = 24)	17 (70.8%)	7 (19.2%)	
No (N = 18)	11 (61.1%)	7 (38.9%)	
Treatment reduction			1.000
Yes (N = 14)	9 (64.3%)	5 (35.7%)	
No (N = 28)	19 (67.9%)	9 (32.1%)	

dose of ribavirin received during the course of treatment and thus impact the treatment outcome. Hence, it is reasonable to expect better SVR rates among patients with the favourable genotypes [9,10,32]. In the Western population, the SVR was 65% [4], even after adding a first generation DAA (Telapravir) to the PEG-IFN and ribavirin combination, while the same treatment combination yielded a SVR rate of 87.7% in an Asian population [33].

In our cohort, there is a significantly higher SVR of 73.8% among patients with hepatitis C genotype 1 infection that is similar to Korea [9] and Taiwan [10]. This may be due to the *IL28B* CC polymorphism prevalent in our predominantly Chinese population [17]. Singapore comprises 74.3% Chinese, 13.3% Malays and 9.1% Indians [13]. Our study had a similar distribution, but the number of Malay (4/42) and Indian (2/42) patients in this study was too small for their results to be generalised across the Singaporean population.

Patients who develop anaemia are also given attenuated doses of ribavirin, which may affect treatment outcome [20]. However, it appears that 70.8% of patients in our population who develop anaemia still manage to achieve SVR. Treatment reduction also did not appear to have an impact on SVR, suggesting that the *IL28B* variants may have a larger impact on SVR than the *ITPA* variants.

One of the limitations of this study is that the sample size for data is relatively small. Our original cohort of 61 patients had a SVR of 73.8%, compared with the 42 patients who agreed to return for genotype testing (with a SVR of 66.7%). This is due to the fact that the group of patients who did not obtain SVR remained on follow-up and were more likely to agree to participate in the study. This small sample size may also underestimate the effects of *ITPA* analysis in the population.

IL28B genotyping can be useful for stratifying treatment of patients in populations with a reasonably high prevalence of *IL28B* CC genotype—and thus a reasonably favourable chance of SVR with conventional treatment in a substantial proportion of patients—and for identifying a smaller subgroup who most likely require the newer direct antiviral agents as their first-line treatment. The estimated cost of new DAA in Singapore is $65 000 to $96 000 for a course of treatment. Further cost effective analysis based on quality of life improvement in years needs to be carried out to determine if patients should first be screened for *IL28B* polymorphism and stratified according to their genotype for treatment. This remains pertinent regardless of whether the cost is borne by the government or the individual. Analysis needs to be carried out to see if it is cost effective to treat a patient with favourable IL28B genotype with DAAs costing $65 000 to $96 000 for a SVR rate of 95% or PEG-IFN and ribavirin costing $16 000 with a SVR rate of around 70% as first-line therapy for chronic HCV genotype 1 infection.

Information from our study, albeit small, helps us affirm our belief that a significant proportion of the Singaporean population is likely to respond positively to a less expensive treatment option. It will help us positively select a relatively small proportion of patients who will most likely benefit from DAAs as the first-line treatment, namely patients with non-CC IL28B genotype and patients with clinical contraindication for PEG-IFN and ribavirin treatment, thus freeing up resources to where they are most needed. Of course, there is still an option to use DAA as a second-line treatment for a quarter of the patients who do not respond favourably despite having the favourable IL28B genotype. It is widely known that rapid viral response (RVR) following the one-month treatment is a strong predictor of SVR, and failure to achieve early viral response (EVR) after the three-month treatment is a strong predictor of non-SVR, independent of patients' pretreatment status [34]. Added to baseline characteristics, RVR and EVR increased the accuracy for predicting SVR. These patients can be identified by their lack of RVR and/or EVR and thus can be spared a full course of PEG-IFN and ribavirin treatment before switching them to treatment with DAAs [35–37]. We are also reassured, based on available evidence, that the treatment outcomes of the new DAAs do not significantly bias against patients with prior PEG-IFN and ribavirin treatment, thus precluding their prior use [38,39].

In conclusion, while the treatment of hepatitis C has vastly improved with the advent of DAAs, many patients are still unable to afford the newer DAAs. *IL28B* genotyping prior to deciding the treatment course may be the path forward in a population with a favourable *IL28B* prevalence. Further cost-effective analysis needs to be done based on *IL28B* genotypes, and the role of pharmacogenetic testing in the management of patients with chronic hepatitis C needs to be determined in a resource-limited setting.

Conflict of interest statement: none declared.

References

1. Messina JP, Humphreys I, Flaxman A, *et al*. Global distribution and prevalence of hepatitis C virus genotypes. *Hepatology* 2015;**61**:77–87.
2. NIH Consensus Statement on Management of Hepatitis C: 2002. *NIH Consens State Sci Statements* 2002;19:1–46.
3. Bruno S, Cammà C, Di Marco V, *et al*. Peginterferon alfa-2b plus ribavirin for naïve patients with genotype 1 chronic hepatitis C: a randomized controlled trial. *J Hepatol* 2004;**41**:474–81.
4. EASL Recommendations on Treatment of Hepatitis C 2015. *J Hepatol* 2015;63:199–236.
5. Backus LI, Belperio PS, Shahoumian TA, *et al*. Real-world effectiveness of ledipasvir/sofosbuvir in 4365 treatment-naive genotype 1 hepatitis C-infected patients. *Hepatology* 2016;**64**:405–14.
6. Andrieux-Meyer I, Cohn J, de Araujo ES, *et al*. Disparity in market prices for hepatitis C virus direct-acting drugs. *Lancet Glob Health* 2015;**3**:e676–7.
7. Graham CS and Swan T. A path to eradication of hepatitis C in low- and middle-income countries. *Antiviral Res* 2015;**119**:89–96.
8. Rosenthal ES and Graham CS. Price and affordability of direct-acting antiviral regimens for hepatitis C virus in the United States. *Infect Agent Cancer* 2016;**11**:24.
9. Jung CH, Um SH, Kim TH, *et al*. Treatment response and long-term outcome of peginterferon α and ribavirin therapy in Korean patients with chronic hepatitis C. *Gut Liver* 2016;**10**:808–17.
10. Chen JY, Lin CY, Wang CM, *et al*. IL28B genetic variations are associated with high sustained virological response (SVR) of interferon-α plus ribavirin therapy in Taiwanese chronic HCV infection. *Genes Immun* 2011;**12**:300–9.
11. Suppiah V, Moldovan M, Ahlenstiel G, *et al*. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. *Nat Genet* 2009;**41**:1100–4.
12. Kanda T, Nakamoto S and Yokosuka O. Is the use of IL28B genotype justified in the era of interferon-free treatments for hepatitis C? *World J Virol* 2015;**4**:178–84.
13. Department of Statistics MoTI, Republic of Singapore,. Population Trends. 2014.
14. Tanaka Y, Nishida N, Sugiyama M, *et al*. Genome-wide association of IL28B with response to pegylated interferon-alpha

and ribavirin therapy for chronic hepatitis *C.Nat Genet* 2009;**41**:.1105–9.
15. Ge D. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature* 2009;**461**:399–401.
16. Dong ZX, Zhou HJ, Xiang XG, *et al*. IL28B genetic variations are associated with treatment response of patients with chronic hepatitis C in a Chinese Han population. *J Dig Dis* 2015;**16**:90–7.
17. Poon KS, Ho SS, Tang JW, *et al*. Targeting both rs12979860 and rs8099917 polymorphisms with a single-tube high-resolution melting assay for IL28b genotyping. *J Clin Microbiol* 2012;**50**: 3353–5.
18. Fellay J, Thompson AJ, Ge D, *et al*. ITPA gene variants protect against anaemia in patients treated for chronic hepatitis C. *Nature* 2010;**464**:405–8.
19. McHutchison JG, Manns M, Patel K, *et al*. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. *Gastroenterology* 2002;**123**:1061–9.
20. Lo Re V 3rd, Teal V, Localio AR, *et al*. Relationship between adherence to hepatitis C virus therapy and virologic outcomes: a cohort study. *Ann Intern Med* 2011;**155**:353–60.
21. Ledipasvir + sofosbuvir (Harvoni). A therapeutic advance in genotype 1 hepatitis C virus infection, despite uncertainties. *Prescrire Int* 2015;**24**:285–9.
22. Bourliere M, Adhoute X, Ansaldi C, *et al*. Sofosbuvir plus ledipasvir in combination for the treatment of hepatitis C infection. *Exp Rev Gastroenterol Hepatol* 2015;**9**:1483–94.
23. Everson GT, Sims KD, Rodriguez-Torres M, *et al*. Efficacy of an interferon- and ribavirin-free regimen of daclatasvir, asunaprevir, and BMS-791325 in treatment-naive patients with HCV genotype 1 infection. *Gastroenterology* 2014;**146**:420–9.
24. Zhang X. Direct anti-HCV agents. *Acta Pharm Sin B* 2016;**6**:26–31.
25. McDonald SA, Dahlui M, Mohamed R, *et al*. Projections of the current and future disease burden of hepatitis C virus infection in Malaysia. *PLoS One* 2015;**10**:e0128091.
26. Leung N, Chu C, Tam JS. Viral hepatitis C in Hong Kong. *Intervirology* 2006;**49**:23–7.
27. Razavi H, Elkhoury AC, Elbasha E, *et al*. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. *Hepatology* 2013;**57**:2164–70.
28. Chahal HS, Marseille EA, Tice JA, *et al*. Cost-effectiveness of Early Treatment of Hepatitis C Virus Genotype 1 by Stage of Liver Fibrosis in a US Treatment-Naive Population. *JAMA Intern Med* 2016;**176**:65–73.
29. Leidner AJ, Chesson HW, Xu F, *et al*. Cost-effectiveness of hepatitis C treatment for patients in early stages of liver disease. *Hepatology* 2015;**61**:1860-9.
30. Tandon N, Reddy KR, Lefebvre P, *et al*. Mo1030 Direct and Indirect Cost Burden of Chronic Hepatitis C Stratified by Liver Disease Severity in Privately-Insured Patients. *Gastroenterology* 2013;**144**:S-1017.
31. Olmedo DB, Cader SA and Porto LC. IFN-γ gene polymorphisms as predictive factors in chronic hepatitis C treatment-naive patients without access to protease inhibitors. *J Med Virol* 2015;**87**:1702–15.
32. Mi Y, Gao YT, Jiao XL, *et al*. The role of interleukin-28b gene polymorphisms in chinese patients with chronic hepatitis C treated with pegylated interferon and ribavirin. *Hepat Mon* 2014;**14**:e18793.
33. Kawaguchi Y, Iwane S, Kumagai T, *et al*. Efficacy and safety of telaprevir, pegylated interferon α-2b and ribavirin triple therapy in Japanese patients infected with hepatitis C virus genotype 1b. *IntMed* 2015;**54**:2551–60.
34. Martinot-Peignoux M, Maylin S, Moucari R, *et al*. Virological response at 4 weeks to predict outcome of hepatitis C treatment with pegylated interferon and ribavirin. *Antiviral Ther* 2009;**14**:501–11.
35. Tontodonati M, Cento V, Polilli E, *et al*. May some HCV genotype 1 patients still benefit from dual therapy? The role of very early HCV kinetics. *New Microbiol* 2015;**38**:491–7.
36. Huang CF, Yu ML, Kao JH, *et al*. Profound week 4 interferon responsiveness is mandatory for hepatitis C genotype 1 patients with unfavorable IL-28B genotype. *J Clin Virol* 2013;**56**: 293–8.
37. Thornton K, Deming P, Manch RA, *et al*. Is response guided therapy dead? Low cure rates in patients with detectable hepatitis C virus at week 4 of treatment. *Hepatol Int* 2016;**10**: 624–31.
38. Afdhal N, Reddy KR, Nelson DR, *et al*. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med* 2014;**370**:1483–93.
39. Lawitz E, Poordad FF, Pang PS, *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.