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Telaprevir or boceprevir based therapy for chronic hepatitis C infection: Development of resistance-associated variants in treatment failure

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ABSTRACT

The use of triple-therapy, pegylated-interferon, ribavirin and either of the first generation hepatitis C virus (HCV) protease inhibitors telaprevir or boceprevir, is the new standard of care for treating genotype 1 chronic HCV. Clinical trials have shown response rates of around 70–80%, but there is limited data from the use of this combination outside this setting. Through an expanded access programme, we treated 59 patients, treatment naïve and experienced, with triple therapy. Baseline factors predicting treatment response or failure during triple therapy phase were identified in 58 patients. Thirty seven (63.8%) of 58 patients had undetectable HCV RNA 12 weeks after the end of treatment. Genotype 1a ($p = 0.053$), null-response to previous treatment ($p = 0.034$), the rate of viral load decline after 12 weeks of previous interferon-based treatment ($p = 0.033$) were all associated with triple-therapy failure. The most common cause of on-treatment failure for telaprevir-based regimens was the development of resistance-associated variants (RAVs) at amino acids 36 and/or 155 of HCV protease ($p = 0.027$) whereas in boceprevir-based regimens mutations at amino acid 54 were significant ($p = 0.015$). SVR12 rates approaching 64% were achieved using triple therapy outside the clinical trial setting, in a patient cohort that included cirrhotics.

1. Introduction

Pegylated-interferon plus ribavirin (pIFN/RBV) has been the standard of care for treating HCV infection. The goal of therapy was achieving a sustained virological response (SVR), defined as undetectable HCV RNA viral load (VL) 24 weeks after completion of treatment considered tantamount to cure. SVR varies between HCV genotypes, with genotype-1-infected patients achieving SVR rates of 40–50% (Fried et al., 2002; Manns et al., 2001; McHutchison et al., 2009) compared with 70–80% in patients with other genotypes. In addition to HCV genotype, the strongest predictors of SVR include baseline VL, the absence of cirrhosis or advanced fibrosis, single nucleotide genetic polymorphisms (SNPs) near the IL28B gene on chromosome 19, prior interferon response and other host factors including age and race (Afdhal et al., 2011).

Several new classes of drugs directly targeting HCV are under development. Recently approved drugs inhibiting HCV NS3/4A protease are a major step towards improving SVR rates and decreasing treatment time in genotype-1-infected patients. Clinical trial data in patients given the first-generation direct-acting antivirals (DAAs) NS3-4A protease inhibitors (PI), telaprevir or boceprevir, combined with pIFN/RBV (triple therapy) have shown treatment length can be shortened in rapid viral responders. SVR rates >80% have been reported (Bacon et al., 2011; Jacobson et al., 2011; Poordad et al., 2011; Zeuzem et al., 2011).

Treatment failure occurs in the setting of poor interferon responsiveness, allowing for the emergence of resistance-associated variants (RAVs). Population and ultra-deep sequencing data suggest that resistant variants are selected in most treatment failure patients. The role of baseline screening for resistance-associated HCV variants before DAA therapy is not clear.

At the Royal Free Hospital, London, UK, we provide tertiary care for a large cohort of HCV-infected patients. Through an expanded access programme prior to approval by the National Institute for

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Health and Clinical Excellence (2012), 59 patients commenced triple therapy with telaprevir or boceprevir and pIFN/RBV. We present data on the outcome of treatment, demonstrate the impact of HCV VL monitoring during therapy and identify parameters associated with outcome.

2. Materials and methods

2.1. Patients

Between June 2011 and May 2012, 59 patients commenced triple therapy; one patient was lost to follow-up. Fifty eight patients returned for at least one follow-up visit and were included in the analyses; Table 1 shows their demographic details. Based on prior treatment, responder/relapsers (RR) cleared HCV RNA at the end of treatment but relapsed during follow-up; virological breakthrough (VB) patients cleared HCV RNA on treatment but RNA became detectable prior to stopping treatment; partial responders (PR) achieved a >2 $\log_{10}$ drop in HCV VL but failed to clear RNA and null-responders (NR) achieved a maximum HCV RNA decrease of <2 $\log_{10}$. One patient (1.7%) was co-infected with HIV-1. All patients were negative for hepatitis B surface antigen. The presence of cirrhosis was confirmed by a liver biopsy revealing either Metavir stage 4 (Bedossa and Poynard 1996) or Ishak stages 5–6 fibrosis (Ishak et al., 1995). In the absence of prior histologic assessment, the presence of cirrhosis was determined by either transient elastography, liver stiffness >14.5 (Ziol et al., 2005) or by ELF testing, ELF > 9.8 (Parkes et al., 2011) within 6 months of starting therapy.

2.2. HCV VL testing and genotyping

HCV RNA was quantified using a validated in-house real-time PCR (RT-PCR) assay that amplifies a portion of the highly conserved 5′ untranslated region. The assay has a lower limit of quantification of 10 IU/ml and detects but cannot quantify HCV RNA at levels < 10 IU/ml.

HCV genotyping was performed using the Abbott's RealTime RT-PCR assay and in some cases, the Versant LiPA.

2.3. HCV genotypic resistance testing

Testing was performed on the first sample with a viral load >1000 IU/ml where the patient met a definition of treatment failure as described below. Nested PCR amplified a portion of the HCV NS3 region prior to population sequencing. Determination of the presence of RAVs and their clinical significance was performed using geno2pheno (hcv.geno2pheno.org/index.php).

2.4. IL28B genotyping

Human genomic DNA extracted from plasma was tested for SNPs within the IL28B locus (C or T for rs12979860 and G or T for rs8099917) using TaqMan allelic discrimination assay, as previously described (Montes-Cano et al., 2010).

2.5. Response guided therapy

All patients were treated according to the guidance included in the summary of product characteristics of the relevant DAA. Patients were eligible for response guided treatment (RGT) if they met the European Medicines Agency criteria. In telaprevir-based regimens, all patients received an initial 12 weeks of triple therapy. Non-cirrhotic treatment naïve and prior relapsers achieving an extended rapid virological response, eRVR, (undetectable HCV RNA at weeks 4 and 12) were given a further 12 weeks of pIFN/RBV; all other telaprevir patients were given a further 36 weeks of pIFN/RBV. In boceprevir-based regimens, all patients received an initial 4 week pIFN/RBV lead-in. Patients achieving a $\geqslant 1 \log_{10}$ HCV RNA drop commenced triple therapy of pIFN/RBV plus boceprevir. Non-cirrhotic prior relapsers and partial responders received 32 weeks of triple therapy and 12 weeks of pIFN/RBV. All prior null-responders and patients with cirrhosis received 44 weeks of triple therapy. No treatment-naïve patients were given a boceprevir-based regimen.

2.6. Definition of treatment failure

Dose reductions of pIFN or RBV were not classed as failure. Early treatment cessation was not considered as treatment failure if the HCV VL was undetectable when treatment stopped. Reasons for failure included failure to clear HCV RNA by week 12, HCV RNA > 1000 IU/ml at week 4 (telaprevir patients), HCV RNA > 100 IU/ml at week 12 or detectable at week 24 (boceprevir patients) or VL rebound of $\geqslant 1 \log_{10}$ IU/ml from nadir at any time point.

2.7. Statistical analysis

To determine statistical significance of categorical data, p values were calculated using Fisher's exact test, two-tailed; for continuous data the unpaired t test was used and binomial testing performed using the two-tailed sign test. p values of <0.05 were considered to be statistically significant. Results for the patients were analysed as one group rather than separate based on the PI used as there was no significant difference in outcome between telaprevir- or boceprevir-based regimens unless otherwise stated.

Table 1
Baseline characteristics of the patient cohort.

	Virological breakthrough[a] (n = 15)	Partial responders[a] (n = 4)	Responder/relapsers[a] (n = 17)	Null responders[a] (n = 15)	Naïve[a] (n = 7)
Genotype (1a/1b/1/other)	9/5/0/1[b]	2/2/0/0	10/3/2/2[c]	12/3/0/0	3/4/0/0
Telaprevir/boceprevir	8/7	4/0	15/2	12/3	7/0
Median baseline VL > 800,000 IU/ml (%)	8 (53)	2 (50)	5 (29)	14 (93)	6 (85)
Median Baseline VL IU/ml (range)	6.03 (4.47–6.75)	6.02 (5.47–6.79)	6.61 (5.12–7.17)	6.32 (5.63–7.12)	6.48 (5.56–6.78)
Male/female	9/6	3/1	15/2	13/2	2/5
Caucasian/other	10/5	4/0	16/1	14/1	4/3
Cirrhosis (absent/present)	7/8	3/1	9/8	4/11	5/2
Median age (years)	53	56	54	54	60

[a] Previous pIFN/RBV treatment outcomes.
[b] One genotype 3a patient.
[c] One genotype 2 patient and one genotype 2a patient.

Logistic regression was used to investigate the association between response to DAAs and the predictors of interest. Due to small numbers, only those with $p < 0.05$ in univariate analysis were included. The groupings for previous IFN response were also grouped more broadly (virological breakthrough; null responder; partial responder being grouped together).

3. Results

3.1. Triple therapy outcome and the role of RAVs

Of 58 patients, 37 (63.8%) achieved and 21 (36.2%) failed to achieve SVR12 (see Table 2). In 17/21 treatment failures (81%) RAVs not detected at baseline were identified in NS3 at positions T54, V36 and/or R155. Of these 17, 10 developed RAVs at V36 and R155; V36L M or V plus R155K. The remaining seven developed RAVs at a single site; three with V36M, one with V36A, two with R155 K and one T54A.

In the remaining four patients who failed therapy, one stopped at week 4 due to side-effects and was lost to follow-up. Two patients achieved an eRVR but had VB between treatment weeks 12 and 24. No RAVs were detected in the failure samples. The 4th patient had a partial response by week 8 but a VL rebound of >1 $\log_{10}$ at week 12, T54S was detected at baseline and failure; no other RAV was identified.

At treatment failure, mutations at V36 and/or R155 positions were only detected in patients treated with telaprevir ($p \leqslant 0.0001$) whereas boceprevir failure was associated with the presence of mutations at T54 ($p = 0.015$).

Three patients stopped all treatment early due to adverse events associated with $\geqslant 1$ treatment component(s). One stopped pIFN/RBV at week 18 and achieved SVR12, one stopped at week 12 having achieved eRVR but relapsed 3 weeks later with V36M and the 3rd self-reported side-effects, stopped whilst still detectable and was lost to follow-up.

Sequencing of baseline samples taken prior to the start of triple therapy failed to detect the presence of any RAVs using population sequencing or ultradeep-pyrosequencing (data not shown).

3.2. Impact of response to prior IFN/RBV treatment

The number of patients achieving SVR12 when stratified by their previous treatment response differed significantly, $p = 0.023$. Of 15 prior relapsers, 14 (93.3%) achieved SVR12. In contrast, prior null-responders were significantly less likely to achieve SVR12; six of 15 (40%). SVR12 rates in the remaining groups were 10/17 (58.8%) in patients classed as VB, 5/7 (71.4%) in treatment-naives and 2/4 (50%) in the partial responders ($p = 0.62$). In the multivariate analysis, naïve patients were 1.55 times more likely to achieve SVR12 and the group containing the VB, RR and PR patients were 2.70 times more likely to achieve SVR12 than the prior non-responders, see Table 3.

3.3. Treatment dose reductions

Twenty seven (46.6%) patients required pIFN and/or ribavirin dose reductions; thrombocytopaenia ($n = 6$, 10.3%), anaemia ($n = 14$, 24.1%), neutropaenia ($n = 2$, 3.4%), weight loss ($n = 1$, 1.7%), a combination of two or more ($n = 3$, 5.2%) or severe dermatitis and neutropaenia ($n = 1$, 1.7%). Of 31 patients who did not reduce pIFN/RBV, 18 (58.1%) achieved SVR12 compared to 19/27 (70.4%) achieving SVR12 who did reduce pIFN/RBV ($p = 0.42$).

3.4. Cirrhotics v non-cirrhotics

Twenty five patients (43.1%) had evidence of cirrhosis prior to commencing triple therapy. SVR12 rates were 60% (15/25) in cirrhotic patients compared to 66.7% (22/33) in patients without evidence of cirrhosis ($p = 0.78$).

3.5. Differences in response by HCV genotype

Patients infected with non-genotype-1a were more likely to achieve SVR than genotype-1a-infected patients: 16/20 (80%) compared to 20/37 (54.1%) respectively ($p = 0.053$), excluding one unsubtyped genotype-1 infection. Patients who failed triple therapy were significantly more likely to be infected with genotype

Table 2
Characteristics of treatment failures.

Patient[a]	Previous IFN/RBV response[b]	PI[c]	IL28B SNP[d]	Reason for failure	Drug resistant mutations
4	VB	TPV	CT	RNA > 1000 week 4	V36M/V R155K
7	RR	TPV	CT	Rebound > 1 $\log_{10}$ from nadir	V36M
8	RR	TPV	TT	Detectable RNA week 12	V36M R155K
10	NR	BOC	CT	Rebound > 1 $\log_{10}$ from nadir	T54A
13	RR	TPV	CT	Rebound > 1 $\log_{10}$ from nadir	R155K
14	PR	TPV	CT	Rebound > 1 $\log_{10}$ from nadir	V36M R155K
16*	NR	TPV	TT	Rebound > 1 $\log_{10}$ from nadir	None
20	NR	TPV	CT	RNA > 1000 week 4	V36M R155K
22*	PR	TPV	TT	Rebound > 1 $\log_{10}$ from nadir	V36A
24	NR	TPV	TT	Rebound > 1 $\log_{10}$ from nadir	V36L, R155K
26	NR	TPV	TT	RNA > 1000 week 4	V36 V/M R155K
28	RR	BOC	CT	RNA > 100 week 12	T54S at BL and failure
29	Naive	TPV	TT	Rebound > 1 $\log_{10}$ from nadir	V36M/V R155K
33*	Naive	TPV	CT	Rebound > 1 $\log_{10}$ from nadir	None
35	NR	TPV	CT	RNA > 1000 week 4	V36M R155K
40	NR	TPV	CC	Rebound > 1 $\log_{10}$ from nadir	R155K
43	RR	TPV	CT	Detectable RNA week 12	V36M R155K
53	NR	TPV	CT	RNA > 1000 week 4	V36L, R155K
56	NR	TPV	CT	RNA > 1000 week 4	V36M
58*	RR	TPV	CT	RNA > 1000 week 4	Lost to follow-up
60	RR	TPV	CT	Rebound > 1 $\log_{10}$ from nadir	V36M

[a] All patients genotype 1a except those marked with *.
[b] Previous pIFN/RBV treatment outcomes: RR, responder relapser, PR, partial responder, NR, null responder, VB, viral breakthrough.
[c] PI, protease inhibitors; TPV, telaprevir, BOC, boceprevir.
[d] IL28B SNP at rs1297860. EOT, end of treatment.

Table 3
Summary of results and statistical significance.

		Number	SVR12	*p*-value	Multivariate estimates (all)	
					OR (95% CI)	*p*-Value
HCV genotype[a]	1a	37	20	0.053	0.26 (0.06, 1.1) 1.00	0.066
	Non 1a	20	16			
Cirrhotic	25	15	0.78			
Non-cirrhotic	33	22				
Previous pIFN/RBV response	VB	17	10	0.023	2.70 (0.7, 10.5)[b]	0.35
	Relapser	15	14			
	Partial response	4	2			
	Null responder	15	6		1.00	
	Naïve	7	5		1.55 (0.2, 13.5)	
Baseline VL (IU/ml)	⩽800,000 IU/ml	16	13	0.13		
	>800,000 IU/ml	42	24			
Mean baseline VL (log_{10} IU/ml) by treatment outcome	6.39	37	0.058			
	6.41	21				
pIFN/RBV dose	Unaltered	31	18	0.42		
	Altered	27	19			
RVR telaprevir	34	24	0.015			
Non-RVR telaprevir	12	3				
eRVR telaprevir	32	24	0.011			
Non-eRVR telaprevir	14	3				
IL28B SNPs rs12979860	CC	12	11	0.040	9.18 (0.98–86)	0.052
	Non-CC	46	26		1.00	
Mean HCV VL (log_{10} IU/ml) prior pIFN/RBV, patient numbers	Baseline (n = 29)	6.40	16	0.22		
	Week 4 (n = 28)	4.87	17	0.57		
	Week 12 (n = 29)	3.54	17	0.033		
	Week 24 (n = 28)	5.17	17	0.88		
Previous VL nadir < 400 cp/ml	Yes	16	12	0.111		
	No	13	6			

[a] Excludes one genotype 1 patient that was not subtyped.
[b] Includes relapse and partial responder. pIFN/RBV, previous pegylated interferon-ribavirin treatment. VL, viral load. VB, virological breakthrough. RVR, rapid virological response. eRVR, extended rapid virological response.

1a compared to 1b, 17/21 (81%) versus 4/21 (19%) respectively (p = 0.007). By multivariate analysis the likelihood of achieving SVR12 was almost fourfold lower in genotype-1a-infected patients, see Table 3.

3.6. Baseline viral load

Of 16 patients with a low baseline VL, ⩽800000 IU/ml, 13 (81.3%) achieved SVR12 compared to 24/42 patients (57.1%) with a high baseline VL, >800,000 IU/ml (p = 0.13). In the patients who achieved SVR12 the median baseline VL, 1,562,920 IU/ml (SE 388,645), was lower compared to those who failed triple therapy 2,636,650 IU/ml (SE 840,608) p = 0.058.

3.7. RVR and eRVR

In telaprevir-based regimens, achieving an RVR, undetectable HCV RNA after 4 weeks of triple therapy, has been associated with a successful treatment outcome (Poordad et al., 2008). In 46 patients on telaprevir, 24/34 patients (70.6%) who achieved an RVR subsequently achieved SVR12, compared to only 3/12 patients (25%) who failed to achieve an RVR (p = 0.015). Twenty-four of 32 patients (75%) who achieved an eRVR also achieved SVR12 compared to 3/14 patients (21.4%) who did not (p = 0.011). Nine of 10 boceprevir-based patients (90%) who achieved an eRVR (undetectable VL at weeks 8 and 20), achieved an SVR12 compared to 1/2 patients without an RVR or eRVR, numbers too small for significance.

3.8. IL28B SNP genotypes

Twelve of 58 patients (20.7%) had the favourable CC genotype at rs12978860 compared to 38/58 (65.5%) with the CT genotype and 8 (13.8%) with the TT genotype. Eleven of 12 patients (91.7%) with the CC genotype achieved SVR12 compared to 22/38 patients with the CT genotype (57.9%) and 4/8 patients with the TT genotype (50%); (p = 0.04 for CC vs non-CC, 0.039 for CC vs CT and 0.11 for CC vs TT). By multivariate analysis, CC genotype patients were over nine times more likely to achieve SVR12 than non-CC genotype patients, see Table 3.

3.9. VL decline during previous IFN/RBV treatment as a predictor of triple therapy outcome

Instead of grouping patients based on prior IFN/RBV responses, we plotted their VL decline from previous IFN/RBV treatment to determine if this could predict triple therapy outcome. We analysed VL levels from 29 patients during prior IFN/RBV treatment to identify differences in the VL decay in patients who did not achieve SVR12 on triple therapy compared to those who did (Fig. 1). During prior IFN/RBV treatment there was no significant difference in the median VL at baseline, week 4 or 24 of treatment between patients who failed triple therapy (n = 12), and those achieving SVR12 (n = 17) p = 0.22, 0.57 and 0.88, respectively. However, at week 12 of previous IFN/RBV treatment the mean VL was significantly higher in patients who subsequently failed to achieve SVR12 on PI-based triple therapy (p = 0.033; Fig. 1). In these 29 patients at week 12 of previous IFN/RBV treatment, 15/17 (88.2%) who achieved SVR12 on triple therapy had an HCV RNA of <400 IU/ml compared to 5/12 patients (41.7%) who failed to achieve SVR12 on triple therapy (p = 0.014).

4. Discussion

In this prospective cohort of triple therapy-treated patients we have shown that most patients who do not achieve SVR12 develop detectable RAVs at treatment failure. In addition we have confirmed the relevance of several variables known to impact on treatment outcome including HCV genotype, baseline VL and VL decay during previous IFN/RBV therapy (Table 3).

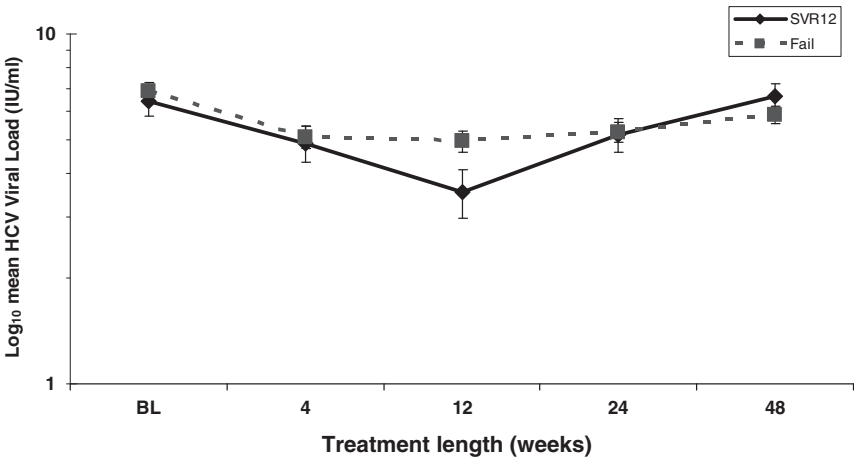

Fig. 1. The mean reduction of HCV viral load (VL, ±SE) over time during the previous Pegylated-Interferon/Ribavirin treatment ($n = 29$) stratified by SVR12 outcome on subsequent triple therapy.

Of the 21 patients who failed triple therapy, development of RAVs associated with drug resistance emerged in 12 during treatment, and in five after completing treatment. Treatment failure during or by 12 weeks post triple therapy (the next scheduled test point), was associated with dual RAVs at positions V36 and R155. These combined RAVs were detected in nine patients compared to a single RAV at V36 or R155 alone in three patients. However patients who failed after 24 weeks of treatment were more likely to do so with RAVs at a single site, V36 M, R155 K or T54A ($n = 4$) compared to 1 with V36M/R155K. One patient completed the triple therapy stage prior to prematurely stopping all therapy. Detection of the V36M mutation post-treatment cessation suggests that this patient would have failed during the pIFN/RBV phase of treatment. During previous pIFN/RBV treatment, this patient cleared HCV RNA at week 12 but relapsed at week 24. We did not find a correlation between the presence of RAVs at baseline and SVR rates, either by standard Sanger population sequencing or by ultradeep-pyrosequencing at a level of 1% (data not shown).

These findings are comparable with those from clinical trials and *in vivo* cell culture data that have shown that the development of resistance mutations at V36 and R155 are associated with telaprevir failure in genotype-1a (Kieffer et al., 2007; Pawlotsky, 2011; Welsch et al., 2008). Although the association of the T54A mutation with resistance to boceprevir has been reported, the T54S mutation has not, Susser et al. (2009) reported no correlation between its detection and treatment outcome.

The median time to treatment failure was 12 weeks; however, the majority of patients were only tested for HCV RNA at weeks 4 and 12. Had all patients been tested at week 8, 2 failure patients could have been identified earlier with potential cost savings of ~£7400 on telaprevir alone (National Institute for Health and Clinical Excellence, 2012). Earlier detection of RAVs may also prevent the development of more complex adaptive mutations that potentially restore a degree of replicative fitness. *In vitro* work with V36M and/or R155K mutations has demonstrated lower fitness than their wild-type counterparts. However, the recent identification of transmission of an HCV strain with the V36M/R155K mutations suggests that this variant retains sufficient replicative capacity to enable it to establish a new infection in the host (Li et al., 2012). The implications for this in terms of future treatment are unknown but in two recent studies where patients who failed previous PI-based regimens with RAVs were retreated with the same PI, the failure rate was around 50% (Lenz et al., 2012; Sarrazin et al., 2013).

The pIFN/RBV components of triple therapy are associated with side effects that may necessitate dose modifications (EASL, 2011). We have shown that reduction of ribavirin and/or pIFN did not significantly affect treatment success, although patient numbers were small. Treatment modifications to pIFN/RBV components were not made until after week 4 of triple therapy (median week 8 for interferon and week 12 for ribavirin reductions) to maximise the antiviral impact of pIFN/RBV as the first 4 weeks is the period when PI resistance is most likely to occur (Forestier et al., 2007; Rong et al., 2010; Welsch et al., 2008).

SNPs at rs12979860 and rs8099917 sites near the IL28B gene are strongly associated with spontaneous HCV RNA clearance or SVR on pIFN/RBV (Ge et al., 2009; Suppiah et al., 2009; Tanaka et al., 2009; Thomas et al., 2009). Polymorphisms at rs12979860 have proven to be the most important genetic predictor for treatment outcome, the most favourable genotype being CC. Polymorphisms at rs8099917 are also useful in predicting SVR with unfavourable outcomes seen with GG or GT genotypes (Afdhal et al., 2011). IL28B SNPs correlated closely with SVR12 in our cohort; CC favourably predicted response. Nonetheless, of the three patients with unfavourable TT/GG genotype at rs1297860 and rs8099917 respectively, two achieved SVR12 indicating that the IL28B genotype should not be used as the sole determinant in identifying patients to be treated with interferon-based therapy.

There was a relationship between the patient's previous IFN/RBV treatment history and SVR12 rates. However, as not all patients had similar VL decay profiles, we examined the VL decay of 29 patients previously treated with IFN/RBV to determine if this could provide a better determinant of triple therapy outcome. This may indicate that the rate of VL decay during previous IFN/RBV treatment rather than the absolute outcome may help predict the outcome of future pIFN/RBV-based regimens. This conclusion warrants further investigation in patients undergoing future pIFN/RBV-based treatment regimens.

This study demonstrates that SVR12 rates of PI-based triple therapy in a conventional clinical setting are in line with those in clinical trials. Our patient cohort had a greater number of cirrhotic patients and one with HIV co-infection, although the relatively small number of patients may have skewed the statistical analysis of the data.

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