Antiviral Research 105 (2014) 112–117

Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

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

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ARTICLE INFO

Article history:
Received 2 January 2014
Revised 19 February 2014
Accepted 23 February 2014
Available online 1 March 2014

Keywords:
HCV
Telaprevir
Protease inhibitors
Drug resistance

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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http://dx.doi.org/10.1016/j.antiviral.2014.02.019
0166-3542/

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.