UK consensus guidelines for the use of the protease inhibitors boceprevir and telaprevir in genotype 1 chronic hepatitis C infected patients

P. Ramachandran*, A. Fraser*, K. Agarwal†, A. Austin‡, A. Brown§, G. R. Foster¶, R. Fox**, P. C. Hayes††, C. Leen‡‡, P. R. Mills§§, D. J. Mutimer¶¶, S. D. Ryder*** & J. F. Dillon†††

*Department of Gastroenterology, Aberdeen Royal Infirmary, Aberdeen, UK.
†Institute of Liver Studies, King's College Hospital, London, UK.
‡Royal Derby Hospital, Derby Hospitals NHS Foundation Trust, Derby, UK.
§Hepatology and Gastroenterology, Imperial College London, London, UK.
¶Centre for Digestive Diseases, Barts and The London School of Medicine and Dentistry, London, UK.
**Brownlee Centre, Gartnavel General Hospital, Glasgow, UK.
††Centre for Liver and Digestive Diseases, Royal Infirmary of Edinburgh, Edinburgh, UK.
‡‡Regional Infectious Diseases Unit, Western General Hospital, Edinburgh, UK.
§§Gartnavel General Hospital, Glasgow, UK.
¶¶Liver Unit, Queen Elizabeth Hospital, Birmingham, UK.
***Queens Medical Centre, Nottingham University Hospitals NHS Trust, Nottingham, UK.
†††Biomedical Research Institute, University of Dundee, Ninewells Hospital, Dundee, UK.

Correspondence to:
Dr P. Ramachandran, Department of Gastroenterology, Ashgrove House, Aberdeen Royal Infirmary, Aberdeen, AB25 2ZN, UK.
E-mail: p_ramachandran@GRO-C

Publication data
Submitted 18 December 2011
First decision 19 December 2011
Resubmitted 30 December 2011
Accepted 31 December 2011
EV Pub Online 1 February 2012

SUMMARY

Background
The nonstructural 3 serine protease inhibitors (PIs), boceprevir and telaprevir, represent the first in a new generation of directly acting antivirals against genotype 1 hepatitis C (HCV) infection. When used in combination with pegylated interferon and ribavirin, these drugs greatly improve sustained virological response rates in both treatment-naïve patients and patients who have had previous virological failure on treatment. However, the addition of these new agents will increase the complexity of therapeutic regimens, the rates of side-effects and costs.

Aims
To review concisely the current evidence and to suggest current best practice, for the use of telaprevir and boceprevir in the management of chronic genotype 1 HCV infection.

Methods
These guidelines for the use of boceprevir and telaprevir have been formulated following extensive review of the current literature, are based on the consensus opinion of a panel of national experts, and have been openly discussed and debated at a national meeting of HCV care providers.

Results
We have made recommendations on a number of the key practical issues facing HCV care providers: (i) Which patients to treat?; (ii) Standards for the provision of care; (iii) Pre-treatment considerations; (iv) Which treatment regimens to use?; (v) Stopping rules; and (vi) Management of adverse effects. Finally, we have produced suggested algorithms for the assessment and treatment of these patients.

Conclusions
These UK Consensus guidelines indicate the current best practice for the use of boceprevir and telaprevir in the management of genotype 1 chronic HCV infection.

Aliment Pharmacol Ther 2012; **35**: 647–662

doi:10.1111/j.1365-2036.2012.04992.x

INTRODUCTION

Chronic hepatitis C infection (HCV) affects around 200 million people worldwide.[1, 2] It is estimated that up to 30% of these patients will develop cirrhosis[3] and around 5% per year will develop decompensated liver disease or hepatocellular carcinoma.[4] Furthermore, chronic HCV infection remains one of the principal indications for liver transplantation, with an increasing incidence in the Western world.[5] Therefore, HCV infection already represents a major health burden, which is predicted to increase several fold in the next two decades.[6] Currently, there are six HCV genotypes recognised with several subtypes identified. Genotype 1 infection (subtypes 1a and 1b) represents the commonest cause of chronic infection in the world.[7]

The advent of dual therapy with pegylated interferon-α (IFN-α) and ribavirin resulted in a vast improvement in the treatment for chronic HCV infection. The current measure of successful therapy is to achieve a sustained virological response (SVR), defined as an undetectable serum HCV RNA level, 24 weeks after cessation of treatment. An SVR is typically associated with resolution of liver disease and improved quality of life in noncirrhotic patients, although cirrhotic patients may still be at risk of liver-related complications. The current standard of care (SoC) treatment for genotype 1 infected patients, with pegylated IFN-α and ribavirin for 48 weeks, is associated with an SVR rate of between 40% and 50% in most clinical trials.[8–10] Although this is a significant advance over single-agent therapy, there remains a large number of patients who will not achieve an SVR. Furthermore, there have been very limited options for those patients who fail to clear the virus with initial dual therapy, retreatment with Peg IFN-α and ribavirin, giving overall SVR rates of only between 10% and 20% in published studies.[11–13] Given the global scale of HCV infection, this remains a significant health problem, and novel therapies are required.

As the life cycle of the HCV virus has become known, novel therapeutic targets have been identified, enabling the development of directly acting anti-viral (DAA) drugs that are more specific than standard treatment regimes. The nonstructural 3 serine protease inhibitors (PIs), telaprevir (Incivo, Janssen-Cilag SpA, Borgo San Michele, Italy) and boceprevir (Victrelis, MSD, Hoddeston, UK), directly inhibit viral replication and may also restore the natural innate immune response of hepatocytes.[14] Large phase 3 trials of both these PIs in patients with chronic infection with genotype 1 HCV have shown highly significant increases in the proportion of patients who obtain an SVR. These drugs have been recognised as a major advance in the treatment of patients infected with genotype 1 hepatitis C virus, and therefore, have been approved for use by the FDA, EMA and Scottish Medicines Consortium (SMC).

These guidelines for the use of boceprevir and telaprevir have been formulated following extensive review of the current literature, are based on the consensus opinion of a panel of national experts, and have been openly discussed at a national meeting of HCV care providers. They aim to concisely summarise the current evidence and to suggest current best practice, for the use of telaprevir and boceprevir in the management of chronic genotype 1 HCV infection.

EFFICACY OF PROTEASE INHIBITOR-BASED THERAPY

A number of high quality clinical trials have now been published, examining the efficacy of the addition of PIs to SoC treatment for both treatment-naïve patients and patients who have had previous virological failure. Evidence only currently exists for the use of these drugs in Genotype 1 infected patients. Furthermore, all the trial data quoted is on an intention to treat basis, including patients who received at least one dose of any study drug.

Treatment-naïve patients

The efficacy of boceprevir in treatment-naïve genotype 1 infected patients has been demonstrated in phase 2 (SPRINT-1)[15] and phase 3 (SPRINT-2)[16] clinical trials. SPRINT-1 included 520 patients who were randomly assigned to one of five groups: PR48 (SoC receiving Peg IFN-α2b 1.5 μg/kg and ribavirin 800–1400 mg daily for 48 weeks); PRB28 or PRB48 (SoC peginterferon-ribavirin and boceprevir 800 mg three times per day for 28 or 48 weeks respectively); PR4/PRB24 or PR4/PRB44 (SoC peginterferon-ribavirin lead-in for 4 weeks followed by triple therapy for 24 or 44 weeks respectively). SVR rates were as follows: PR48 Control = 38%; PRB28 = 54%; PRB48 = 67%; and PR4/PRB24 = 56%; PR4/PRB44 = 75%, indicative of significantly enhanced SVR with the addition of boceprevir (Table 1).

In the phase 3 study, SPRINT-2, all 1097 patients received 4 weeks of lead-in treatment (SoC Peg IFN-α2b 1.5 μg/kg and ribavirin 600–1400 mg daily) followed by randomisation to three groups: Group 1 (control receiving 44 weeks SoC peginterferon-ribavirin and placebo), Group 2 (response-guided therapy with SoC peginterferon-ribavirin and boceprevir 800 mg t.d.s for 24 weeks with those having detectable HCV RNA at any visit between 8 and 24 weeks continuing on SoC peginterferon-ribavirin for

Table 1 | Summary of clinical trial data for the use of boceprevir and telaprevir in treatment-naïve patients

Drug	Boceprevir								Telaprevir						
Trial	SPRINT-1					SPRINT-2			PROVE1			PROVE2		ADVANCE	
	PR48	PRB28	PRB48	PR4+ PRB24	PR4+ PRB44	Gp1	Gp 2 (RGT)	Gp3 (48 weeks)	PR48	T12 PR24	T12PR48	PR48	T12PR24	PR	T8PR	T12PR
SVR	38%	54%*	67%†	56%†	75%†	38%	63%‡	66%‡	41%	61%*	67%†	46%	69%†	44%	69%‡	75%‡
Relapse	24%	30%	7%†	24%	3%†	22%	9%‡	9%‡	23%	2%§	6%§	22%	14%	28%	9%	9%

Summary of the SVR and relapse rates from the stated clinical trials for the addition of boceprevir or telaprevir to SoC therapy for treatment-naïve Genotype 1 HCV-infected patients. Shaded columns indicate control groups receiving SoC treatment alone. Relapse is defined as undetectable HCV RNA at end of treatment, but detectable within 24 weeks of follow-up. Study design and treatment groups are summarised in the text. Statistical analyses are compared with SoC treatment alone. HCV, hepatitis C infection; RGT, response-guided treatment.

* $P < 0.05$.

† $P < 0.01$.

‡ $P < 0.001$.

§ No *P*-value reported.

an additional 20 weeks) and Group 3 (SoC peginterferon-ribavirin and boceprevir for 44 weeks). SVR rates were as follows: Group 1 = 38%; Group 2 = 63%; and Group 3 = 66% (Table 1). Thus, in both phase 2 and phase 3 studies, the addition of boceprevir to standard dual therapy in treatment-naïve patients results in increase SVR rates by a minimum of 25%. Furthermore, the use of response-guided treatment (RGT) with boceprevir is associated with an improved SVR (compared with dual therapy) despite a shorter duration of treatment.

Similar studies have been carried out for telaprevir in patients with genotype 1 chronic HCV infection. In the PROVE1 study,[17] 233 patients received one of the following three treatments: PR48 (SoC Peg IFN-α2a 180 μg/week and ribavirin 1000–1200 mg daily for 48 weeks), T12PR24 and T12PR48 (Telaprevir for 12 weeks with SoC peginterferon-ribavirin followed by SoC peginterferon-ribavirin alone for 12 and 36 additional weeks respectively). SVR rates were as follows: PR48 = 41%, T12PR24 = 61% and T12PR48 = 67% (Table 1). Similar findings were seen in PROVE2,[18] where SVR rates for PR48 (control) and T12PR24 groups were 46% and 69% respectively (Table 1). Importantly, both PROVE1 and PROVE2 studies demonstrated that shortening the duration of peginterferon-ribavirin to 12 weeks to match duration of telaprevir therapy reduced SVR to that of standard dual therapy.[17, 18] Furthermore, in a separate treatment arm, PROVE2 showed that ribavirin was essential to reduce the risk of relapse and viral breakthrough with telaprevir treatment.[18]

In the phase 3 ADVANCE study,[19] a total of 1088 patients were randomised to three treatment groups: PR group (SoC Peg IFN-α2a 180 μg/week and ribavirin 1000–1200 mg daily for 48 weeks), T8PR and T12PR groups (SoC peginterferon-ribavirin and telaprevir for 8 or 12 weeks, respectively, followed by SoC peginterferon-ribavirin alone in a response-guided manner, with patients who had an eRVR (negative HCV RNA at 4 and 12 weeks) continuing treatment up to week 24, whereas those who had positive HCV RNA at either 4 or 12 weeks continuing SoC peginterferon-ribavirin treatment up to week 48. The SVR rates were as follows: PR group = 44%, T8PR = 69% and T12PR = 75% (Table 1). Thus, overall, addition of telaprevir to standard dual therapy regimens in treatment-naïve patients results in improved SVR rates by at least 20–25%, a similar efficacy to boceprevir-based regimens.

In conclusion, phase 2 and 3 studies using boceprevir and telaprevir in treatment-naïve patients in addition to peginterferon-ribavirin, shows a robust increase in overall

SVR rates of at least 20–25%. Whilst the regimens used differ between studies, the efficacy of boceprevir and telaprevir is largely similar. Furthermore, in the larger phase 3 studies (SPRINT-2 and ADVANCE), response-guided therapy seems equally effective and may enable shortened treatment durations in specific groups of patients. In addition, the SVR rates have been improved in the phase 3 compared with phase 2 studies, indicative of better management of adverse effects and higher concordance rates as a result of improved physician experience and education.

Patients who have had virological failure with previous treatment

As discussed above, a significant proportion of patients will not achieve an SVR with current SoC treatment due to virological failure. These patients can broadly be divided into three groups:

(i) Virological relapse: Patients who have undetectable HCV RNA at the end of treatment, but do not achieve an SVR (i.e. detectable HCV RNA during follow-up period).

(ii) Virological partial response: Patients who have a ≥ 2 $\log_{10}$ IU/mL drop in HCV RNA by 12 weeks of treatment, but never achieve undetectable HCV RNA

(iii) Virological null response: Patients who have a <2 $\log_{10}$ IU/mL drop in HCV RNA by 12 weeks of treatment

Phase 2 and 3 studies have now been conducted using boceprevir and telaprevir in these patients who have not achieved an SVR despite prior treatment with combination antiviral therapy. In the RESPOND-2 study using boceprevir,[20] a total of 403 patients with previous relapse and partial response were recruited. Patients with previous null response were not included in this study. All patients received a lead-in treatment for 4 weeks with SoC Peg IFN-α2b 1.5 μg/kg weekly and ribavirin 600–1400 mg daily. Patients were then randomised to three groups: Group 1 [control received SoC peginterferon-ribavirin for 44 additional weeks (total 48 weeks)] and Group 2 [response-guided therapy with all patients receiving SoC peginterferon-ribavirin and boceprevir for 32 additional weeks (up to week 36); those patients with undetectable HCV RNA at week 8 and 12 completed therapy at week 36, whereas those patients who had detectable HCV RNA at week 8 (but not at week 12) continued on SoC peginterferon-ribavirin until week 48]; Group 3 (SoC peginterferon-ribavirin and boceprevir for an additional 44 weeks). Overall SVR rates were Group 1 (control) = 21%, Group 2 (response-guided therapy) = 59% and Group 3 = 66%. Subgroup analysis indicated SVR rates (group 1 vs. 2 vs. 3) among patients with previous relapse of 29% vs. 69% vs. 75% and among patients with previous partial response of 7% vs. 40% vs. 52% (Table 2).

In the REALISE study using telaprevir,[21] 663 patients with previous relapse, partial response and null response were randomised to three groups: PR48 (control group receiving SoC Peg IFN-α2a 180 μg/week and ribavirin 1000–1200 mg daily for 48 weeks), T12PR48 (receiving SoC peginterferon-ribavirin for 48 weeks with telaprevir treatment for the first 12 weeks) and lead-in T12PR48 (4 weeks lead-in with SoC peginterferon-ribavirin followed by 12 weeks triple therapy, then continuation on SoC peginterferon-ribavirin for a total of 48 weeks). Overall SVR rates were PR48 = 17%, T12PR48 = 64% and lead-in T12PR48 = 66%. Subgroup analysis indicated SVR rates (PR48 vs. T12PR48 vs. lead-in T12PR48) among patients with prior relapse of 24% vs. 83% vs. 88%; among patients with prior partial response of 15% vs. 59% vs. 54%; and among patients with prior null response of 5% vs. 29% vs. 33% (Table 2).

In summary, there is a significant benefit to retreating patients who have previously had virological failure with peginterferon-ribavirin therapy, using triple therapy with a protease inhibitor. Overall, this can improve SVR rates in these patients by over 40%. The benefits of protease inhibitor regimens over SoC treatment seem to hold for patients with prior relapse, partial response and null response, although the SVR rate is lower in prior partial responders and null responders. The regimens used for boceprevir and telaprevir differed between the studies, but showed similar SVR rates. Of note, boceprevir has not been used in patients with a prior null response.

Patients with nongenotype 1 HCV infection

Currently, there are very limited data for the use of DAAs in patients with nongenotype 1 HCV infection. Only a small proof of concept study has suggested some efficacy of telaprevir in Genotype 2 HCV infection, albeit fewer than 20 patients received the PI.[22] Therefore, currently neither boceprevir nor telaprevir should be used in patients with nongenotype 1 HCV infection.[23] Such patients may benefit from the ongoing development of the next generation of DAAs.

COST-EFFECTIVENESS OF PI TREATMENT

Clearly, the addition of PI treatment to the current SoC treatment of pegylated intereferon and ribavirin represents a major step forward in the treatment of genotype

Table 2 | Summary of clinical trial data for the use of boceprevir and telaprevir in patients who had virological failure with previous treatment

Drug	Boceprevir						Telaprevir					
Trial	RESPOND-2						REALISE					
Previous response	Relapse			Partial response			Relapse			Partial response			Null response		
	Group 1	Group 2 (RGT)	Group 3 (48 weeks)	Group 1	Group 2 (RGT)	Group 3 (48 weeks)	PR48	T12 PR48	Lead-in T12PR48	PR48	T12 PR48	Lead-in T12PR48	PR48	T12 PR48	Lead-in T12PR48
SVR	29%	69%*	75%*	7%	40%*	52%*	24%	83%*	88%*	15%	59%*	54%*	5%	29%*	33%*
Relapse	NR	NR	NR	NR	NR	NR	65%	7%†	7%†	N/A	21%	25%	60%	27%†	25%†

Summary of the SVR and relapse rates, where quoted, from the stated clinical trials for the addition of boceprevir or telaprevir to SoC therapy for Genotype 1 HCV-infected patients who have had prior virological failure with treatment. Patients are divided into those with prior relapse (undetectable HCV RNA at the end of treatment but do not achieve an SVR), prior partial response (≥ 2 $\log_{10}$ IU/mL drop in HCV RNA by 12 weeks of treatment but never achieve undetectable HCV RNA) or prior null response (< 2 $\log_{10}$ IU/mL drop in HCV RNA by 12 weeks of treatment). Shaded columns indicate control groups receiving SoC treatment alone. Relapse is defined as undetectable HCV RNA at end of treatment, but detectable within 24 weeks of follow-up. Study design and treatment groups are summarised in the text. Statistical analyses are compared with SoC treatment alone. HCV, hepatitis C infection; NR, No data reported; RGT, response-guided treatment; SVR, sustained virological response.

* $P < 0.001$.

† No *P*-value reported.

1 chronic HCV infection. Viral eradication at any stage of liver disease, both cirrhotic and noncirrhotic, prevents disease progression and improves survival and quality of life whilst reducing the healthcare costs associated with the management of complications. However, PIs remain costly, boceprevir costing £2800 per month and telaprevir costing £7466 per month of treatment.[1] Thus, a full treatment course of telaprevir (12 weeks fixed-duration) will cost £22 398, whereas a full treatment course of boceprevir will range from to £16 800 to £30 800 depending on the regimen used for a particular patient.

Full cost-effectiveness analyses are starting to emerge. The addition of boceprevir in treatment-naïve patients in SPRINT-2 regimens yielded an incremental cost-effectiveness ratio (ICER) of $24 017 for RGT treatment and $39 733 for fixed-duration treatment compared with SoC.[24] In treatment-experienced patients, managed according to RESPOND-2 regimens, the addition of boceprevir yielded an ICER of $27 900 for RGT and $33 395 for fixed-duration therapy when compared with peginterferon and ribavirin alone.[25] Similar data has been shown in an independent analysis by the Scottish Medicines Consortium (http://www.scottishmedicines.org.uk), where the ICERs of boceprevir in treatment-naïve patients were £18 225 (F0–F3 hepatic fibrosis) and £20 808 (F4 cirrhosis), whereas in treatment-experienced patients, ICERs were £15 668 (F0–F3 hepatic fibrosis) and £1683 (F4 Cirrhosis). Thus, from these initial analyses, boceprevir treatment seems to be cost-effective at current thresholds, in particular, for cirrhotic treatment-experienced patients and the use of RGT in either treatment-naïve patients or patients with previous virological failure. Given the similar efficacy and overall costs, these data are likely to be replicated with telaprevir. Interestingly, in a separate study, a cost-effectiveness analysis of the addition of telaprevir to peginterferon-ribavirin in genotype 1 infected patients with IL-28B CC genotype (high chance of cure with SoC regimes) demonstrated a lack of cost-effectiveness for the use of telaprevir in this group.[26] Thus, it is likely that in subgroups of patients who have a high chance of achieving an SVR with SoC therapy alone, the addition of a PI will not prove to be cost-effective at current thresholds.

Mathematical modelling has demonstrated that by increasing the cure rate to 80% and by treating 50% of HCV-infected patients, there will be a significant reduction of 34% in deaths due to liver disease.[6] Achieving

[1]List prices obtained from National Electronic Library for Medicines (http://www.nelm.nhs.uk/en/).

such figures will have a massive impact on the disease burden in forthcoming years. Whilst, by addition of a PI, SVR rates can approach this 80% in certain groups, the number of patients being treated must continue to increase to make a meaningful impact at a population level.

FACTORS PREDICTIVE OF RESPONSE TO TREATMENT

Prior to deciding on appropriate treatment regimens, it is possible to predict those patients who are highly likely to respond to therapy (good response group) and those who are less likely to respond (poor response group). This will enable a more tailored approach to therapy. In HCV genotype 1 patients, 67–75% can now be cured, 38–46% can be cured with SoC alone, an additional 23–31% with the use of a PI, whereas 25% will still have treatment failure. If we had predictors that accurately identified these groups, therapy could, potentially, be made more cost-effective, and some patients would be spared unnecessary side-effects. Perfect predictors do not exist currently. However, it is possible to identify a subset of patients who have very high SVR rates with SoC alone, in whom the addition of a PI may have little additional benefit. These patients can be predicted on the basis of combinations of baseline clinical, viral and genetic characteristics.[27–30] Alternatively, early viral response to peginterferon-ribavirin has high positive predictive value for cure and applies to a larger proportion of patients.[31, 32] However, the appropriate duration of therapy for such patients is still debated: a reduced duration of 24 weeks has been suggested from retrospective cohorts to show SVRs ranging from 80% to >90%,[33] whereas the trials of triple therapy have prospectively demonstrated SVRs of >90% with 6 months therapy.

Additionally, a number of characteristics associated with a poor SVR rate have been reported in the recent phase 3 PI studies (see Table 3). These are largely in keeping with previous data generated from SoC studies.[7, 27] Furthermore, recent subgroup analysis has identified a reduction in HCV RNA levels of <1 $\log_{10}$ after 4 weeks of lead-in peginterferon-ribavirin as a significant predictor of a reduced SVR rate, even with triple therapy.[16, 34] This is particularly low in patients with coexistent cirrhosis.

Thus, by considering a number of baseline factors and monitoring the early viral response to peginterferon-ribavirin, it is possible to identify patients in the good response group who would gain little benefit from the addition of a PI, and those in the poor response group who may still have a low chance of cure even with the use of a PI and might be better served to await treatment with the next generation of DAAs.

Table 3 | Factors predisposing genotype 1 patients to a reduced likelihood of achieving an SVR with PI-based triple therapy

Major factors	
High baseline HCV RNA levels (>800 000 IU/mL in most studies)	
Presence of advanced fibrosis or cirrhosis	
Adverse IL-28B genotype (CT/TT)	
In previous treatment-failure patients: prior null response	
Post-treatment initiation: reduction of <1 $\log_{10}$ IU/mL of HCV RNA after lead-in 4 weeks of peginterferon-ribavirin alone	
Minor factors	
Age (>40–45)	High BMI (>30)
Ethnic origin (Black vs. Nonblack)	Presence of Type 2 DM
HCV Genotype 1a	
In previous treatment-failure patents: prior partial response	

Summary of factors that have been shown to be associated with a poor response to protease inhibitor-based triple therapy. Factors that have a dominant effect have been classified as major factors. HCV, hepatitis C infection; SVR, sustained virological response.

VIRAL RESISTANCE

The existing evidence from the use of DAAs in the treatment of HIV and hepatitis B infection indicates that viral resistance is a major concern. HCV is clearly a different virus, with numerous naturally occurring variants present at any one time as a result of the high replication rate. These variants can confer resistance to DAAs by altering the drug binding site.[35] The administration of DAAs may then lead to the resistant mutant becoming the dominant viral strain, causing virological failure of treatment. Furthermore, these viral strains may subsequently develop additional resistance mutations that may render a class of DAAs redundant, potentially compromising future therapeutic options and the chance of cure. The impact of resistance in HCV to PIs is yet to be delineated.

From the studies to date, it seems that peginterferon and ribavirin administration is critical to preventing HCV resistance to PIs. In early phase 1 studies, monotherapy with either boceprevir[36] or telaprevir[37, 38] was associated with the emergence of viral resistance mutations, which were diminished when the PI was combined with peginterferon. Furthermore, in the SPRINT-2 study,

patients who were less responsive to the lead-in peginterferon-ribavirin phase (<1 $\log_{10}$ decline in HCV RNA by week 4) showed significantly higher levels of virological failure and resistance mutations.[16] In addition, in the PROVE2 study, patients who had treatment with peginterferon and telaprevir without ribavirin showed lower SVR rates, with increased resistant mutations.[18] These data indicate that currently, PIs should only be used in combination with peginterferon and ribavirin to maximise SVR rates and minimise the development of resistance mutations.

Resistance mutations are also more likely to develop with ongoing exposure to PIs when treatment is futile. Thus, all of the studies to date enforce strict stopping rules, based on inadequate virological responses, when PI treatment should be discontinued to prevent ongoing exposure to the drugs when the chance of cure is very low. These rules vary between treatment regimens, but should be robustly adhered to in clinical practice.

The long-term consequences of these resistance mutations remain uncertain. It does seem that the HCV resistant variants decline with time off therapy, and become undetectable in the majority of cases during long-term follow-up.[39, 40] However, it is not clear if further administration of PIs to these patients might lead to rapid re-emergence of the resistant HCV or how they might respond to newer DAAs.

Thus, in the new era of PI therapy for chronic genotype 1 HCV infection, it is important to be aware of the potential for viral resistance, as this might adversely affect patient outcome now and in the future. This can be minimised by strict adherence to therapeutic regimens and stopping rules.

ADVERSE EFFECTS

Whilst the appropriate use of PIs with peginterferon-ribavirin provides significant increases in cure rates of genotype 1 chronic HCV infection, there is also an increased rate of adverse effects with the use of triple therapy.

As indicated (Table 4), the principal side-effects associated with boceprevir treatment are dysgeusia (altered sense of taste), anaemia and neutropenia. The dysgeusia does not usually need any alteration in treatment. Dose reduction of boceprevir should not be used in the management of adverse effects, as suboptimal dose will promote the emergence of resistant species in failing regimens.

With telaprevir treatment regimens, the adverse effect profile is slightly different from boceprevir (Table 5).

Table 4 | Summary of adverse events increased with boceprevir treatment in phase 3 trials

Drug	Boceprevir					
Trial	SPRINT-2			RESPOND-2		
	Group 1	Group 2 (RGT)	Group 3 (48 weeks)	Group 1	Group 2 (RGT)	Group 3 (48 weeks)
Serious adverse event	9%	11%	12%	5%	10%	14%*
Discontinuation due to adverse event	16%	12%	16%	2%	8%	12%*
Anorectal symptoms	NR	NR	NR	NR	NR	NR
Dysgeusia	18%	37%†	43%†	11%	43%†	45%†
Anaemia	29%	49%†	49%†	20%	43%†	46%†
Grade 3 neutropenia (500–750/mm^3)	14%	24%†	25%†	9%	19%	20%*
Rash	23%	25%	24%	5%	17%*	14%
Fatigue	60%	53%	57%	50%	53.7%	57.1%
Pruritus	27%	24%	26%	17.5%	18.5%	19.3%
Nausea	42%	48%	43%	37.5%	43.8%	39.1%
Diarrhoea	22%	22%	27%	15%	22.8%	23%

Summary of principal reported adverse effects in phase 3 studies with treatment arms containing boceprevir. Shaded columns indicate control groups receiving SoC treatment. Statistical analyses are compared with SoC treatment alone. NR, not reported; RGT, response-guided treatment.

* $P < 0.05$.

† $P < 0.001$.

Table 5 | Summary of adverse event increased with telaprevir treatment in phase 3 studies

Drug	Telaprevir						
Trial	ADVANCE			REALISE			ILLUMINATE
	PR	T8PR	T12PR	PR48	T12 PR48	Lead-in T12PR48	T12PR24 and T12PR48
Serious adverse event	7%	9%	9%	5%	12%	12%	9%
Discontinuation due to adverse event	7%	10%	10%	3%	15%	11%	18%
Anorectal symptoms/ haemorrhoids	4%	8%*	13%*	7%	15%*	12%*	NR
Dysgeusia	NR	NR	NR	6%	12%	12%	NR
Anaemia	19%	39%*	37%*	15%	30%*	36%*	39%
Total neutropenia	19%	17%	14%	11%	14%	13%	NR
Rash	24%	35%*	37%*	19%	37%*	36%*	37%
Fatigue	57%	58%	57%	40%	55%	50%	68%
Pruritus	36%	45%*	50%*	27%	52%*	50%*	51%
Nausea	31%	40%	43%	23%	35%	33%	47%
Diarrhoea	22%	32%	28%	14%	25%	26%	30%

Summary of principal reported adverse effects in phase 3 studies with treatment arms containing telaprevir. Shaded columns indicate control groups receiving SoC treatment. Statistical analyses are compared with SoC treatment alone. NR, no data reported.

* No *P*-value reported.

Studies have shown an increase in skin rash (see below) and anorectal symptoms (discomfort and pruritus) with telaprevir treatment. The anorectal symptoms are usually tolerable for the duration of telaprevir treatment, and rarely (0.5%) led to discontinuation.

Anaemia in PI treatment

Treatment with either PI is associated with an increased rate of anaemia compared with SoC. As shown (Table 4), there was a 20–26% increase in the rate of anaemia in boceprevir-treated patients compared with SoC. However, the rate of severe anaemia (Grade 3 or 4: Hb <8 g/dL) remained low with overall rates of 3–7% in boceprevir groups (compared to 1–2% in SoC) with only 2–3% of patients discontinuing treatment due to anaemia (compared with 0–2% in control arms).[16, 20] In boceprevir trials, erythropoietin use was actively encouraged with the provision of free drug to manage anaemia. Furthermore, dose reductions in ribavirin have not been shown to have an adverse effect on SVR rates.

In the telaprevir-treated patients, there was a 15–21% increase in the rate of anaemia compared with SoC (Table 5). The lower anaemia rate may in part reflect the shorter duration of triple therapy with telaprevir compared with boceprevir. Similar rates of severe anaemia (Grade 3 or 4) were seen compared with boceprevir treatment and only resulted in discontinuation of telaprevir in 2–4% of cases.[19, 21, 41] In the studies to date, the use of erythropoietin was not permitted in combination with telaprevir. Importantly, dose reduction of ribavirin is not associated with reduced SVR rates in combination with telaprevir.[42] Interestingly, the appearance of anaemia during treatment with SoC or triple therapy, with either PI, does not have a negative effect on SVR, but rather, has been shown to be positively associated with an increased chance of SVR.

Rash in PI treatment

One of the principal adverse events in telaprevir treatment is rash (Table 5). This leads to discontinuation of telaprevir in 5–7% of cases,[19, 21, 41] at which point the rash invariably resolves (although this may take several weeks). The rash is predominantly eczematous and pruritic. Fifty percent of patients developing rash do so within the first 4 weeks of treatment, although it can occur at any time. Rashes have been divided into:

Mild localised.

Moderate diffuse affecting <50% of body surface area.

Severe affecting >50% surface area or mucous membranes or with systemic symptoms (including SCARs.[2])

[2]Severe Cutaneous Adverse Reactions (SCARs) includes DRESS (drug rash with eosinophilia and systemic symptoms) and Stevens-Johnson Syndrome.

HCV RNA TESTING

In the treatment strategies discussed, particularly when using response-guided therapy (RGT) and assessing stopping rules, a critical requirement for determining ongoing management is undetectable HCV RNA. In the clinical trials, highly sensitive PCR assays were used, with a lower limit of detection of 9.3–15 IU/mL,[15–17, 19–21] which are not always widely available in clinical practice. The use of less sensitive assays with PI treatment may lead to errant classification of HCV RNA as undetectable, which may inappropriately reduce treatment duration or lead to ongoing exposure to PIs when treatment is futile, increasing the risk of resistance mutations. Unsurprisingly, such misclassification would have an adverse effect on SVR rates.[43]

Furthermore, in clinical practice, there is often a delay from the time of sampling to receiving the HCV RNA quantification. When using these RNA titres as treatment decision points, this can cause a delay in initiating changes to therapy, which again may lead to unnecessary exposure to PIs, and hence a higher risk of viral resistance and increased cost. Therefore, rapid turnaround in laboratory assays is required.

CONSENSUS STATEMENTS

Which patients to treat?

(a) Due to the improvements in cure rates and potential for shortened therapy, protease inhibitor-based regimens should be considered for all genotype 1 chronic HCV-infected patients. This is applicable for treatment-naïve patients and patients who have had virological failure following prior exposure to SoC therapy

(i) Where resources determine that there may be a delay in initiation of treatment, priority for PI treatment should be based on clinical need. Specific consideration should be given to patients likely to develop complications in the next 5 years or who have other pressing need for early therapy (e.g. concerns regarding fertility or disabling nonhepatic consequences of infection). Conversely, certain patients with a good liver prognosis may, following discussion, elect to wait for novel therapies.

(b) Nongenotype 1 chronic HCV-infected patients should be treated without a PI, according to SoC regimens.

To prevent the predicted increase in deaths from liver failure and hepatocellular carcinoma due to chronic HCV infection, epidemiology and disease modelling indicates that we need to continue to increase the number of patients treated and cured.[44]

(c) The adoption of PI-based regimens should not reduce the total number of HCV-infected patients being treated and cured.

The provision of care

(a) Due to the importance of RGT and stopping rules in PI-based regimens and the increased risk of adverse effects, the use of PI treatment should be limited to centres providing the following standards of care:

(i) Adherence to national standards for HCV.

(ii) Continuous audit of SVR rates to therapy.

(iii) Continuous audit of treatment discontinuation rates.

(iv) A high level of expertise in the use of antiviral drugs.

(v) Access to viral load estimation results within five working days of sampling.

(vi) Access to HCV PCR with a lower limit of detection of at most 15 IU/mL.[43]

(vii) Access to non-invasive investigations and/or liver biopsy to assess the degree of hepatic fibrosis.

(viii) Sufficient specialised medical and nursing staff to provide year round support to patients on therapy.

(ix) A series of protocols to minimise the risk of developing and to manage adverse reactions to therapy.

(x) A comprehensive and skilled consultation service for patients emphasising the risks and benefits of therapy along with the requirement for adherence.

(b) Where possible, all patients should be invited to participate in ongoing research initiatives (e.g. enrolment to the HCV research UK[3] database).

(c) Ongoing recruitment to clinical trials should continue where feasible.

Pre-treatment considerations

(a) Assessment of likelihood of response.

(i) All patients should have an assessment including baseline viral titres, an assessment of disease stage/cir-

[3]HCV research UK is a Medical Research Council (MRC) funded initiative to create a database and biobank of 10 000 HCV-infected patients for research and quality improvement.

rhosis (using non-invasive means or biopsy) and other demographic factors (see Table 3).

(ii) IL-28B genotyping and subtyping of HCV virus (1a or 1b) have some predictive value for treatment response, and may be used with other data to assist management discussions with patients about therapy, but are not required for treatment decisions.

(iii) In previously treated patients, if the data are available to determine the degree of prior response, this should be used to aid decision on treatment duration.

(b) Co-morbid conditions.

(i) HIV co-infected patients are at risk of rapid liver disease progression. Although no large scale clinical trial data currently exists, relevant drug interactions have been studied and treatment with PIs may be considered by expert physicians on a case-by-case basis, with active recruitment to ongoing clinical trials where available or audit of outcomes.

(ii) Protease inhibitor-based triple therapy can not currently be recommended in patients with decompensated liver disease, hepatitis B co-infection, active cancer or post-transplant due to limited data. The use of protease inhibitor triple therapy regimens in these groups should be the subject of new clinical trials.

(iii) Caution should be exercised in using PI treatment in patients with significant baseline neutropenia ($<1200/mm^3$), thrombocytopenia ($<90\ 000/mm^3$) or anaemia (Hb <12 g/dL for females or Hb <13 g/dL for males).

(iv) Due to potentially dangerous drug–drug interactions, dual peginterferon and ribavirin therapy might be considered more appropriate for some patients where there are serious concerns regarding these interactions with prescribed or illicit medication.

(v) Dual therapy should be considered in conditions that impair adherence to therapy and thus reduce the effectiveness of triple therapy and increase the risk of development of resistance mutations.

(vi) Depression does not appear to be increased with PI treatment, but should be considered and monitored as per SoC treatment regimes.

(c) Drug interactions.

Both boceprevir and telaprevir are metabolised by the CYP450 system, and are therefore prone to a number of drug–drug interactions. Evidence in this area is rapidly accumulating from ongoing studies.

(i) Prior to prescribing a PI, a careful drug history (prescribed and nonprescribed) should be taken and relevant prescribing information and databases (e.g. www.hep-druginteractions.org) should be consulted for any potential drug–drug interactions. Primary Care providers need these issues specifically highlighted to avoid potentially 'toxic' interactions on therapy.

Which treatment regimens to use?

(a) Which peginterferon-ribavirin to use?

The treatment regimens used differ between the two PIs and the different trials. One critical difference between the studies is the use of different peginterferon-ribavirin preparations and doses. In general, in the boceprevir studies, pegylated IFN-α2b (PegIntron; Merck, Whitehouse Station, NJ, USA) at a dose of 1.5 μg/kg once weekly and ribavirin (Rebetol; Merck) at weight-based dose of 600–1400 mg daily in two divided doses were used. In the telaprevir studies, pegylated IFN-α2a (Pegasys; Roche, Welwyn Garden City, UK) at a dose of 180 μg/week and ribavirin (Copegus; Roche) at a weight dependent dose of 1000 mg (<75 kg) or 1200 mg ($\geq$75 kg) per day were used. Direct comparison studies between Peg IFN-α2a and Peg IFN-α2b in SoC treatment have not shown any significant difference in overall response rates.[10] Furthermore, in small studies, telaprevir has been used with Peg IFN-α2b[45] and boceprevir with IFN-α2a[46] with no detrimental effect.

(i) Peg IFN-α2a or Peg IFN-α2b can be used interchangeably with either telaprevir or boceprevir according to local preferences.

(ii) Ribavirin brands can be used interchangeably in treatment regimens.

(b) Which protease inhibitor to use?

The documented evidence clearly shows a benefit for the use of either boceprevir or telaprevir as part of a triple therapy regimen in both treatment-naïve patients and patients with previous virological failure. Largely, the magnitude of beneficial effect is similar for either drug. No direct comparison studies between boceprevir and telaprevir have been conducted, and thus, neither drug can be recommended over the other. However, specific characteristics of each drug may lead to their use in certain circumstances. Boceprevir-based regimens use a 4-week lead-in with peginterferon-ribavirin, which may offer extra information on treatment tolerability and the likelihood of achieving an SVR. In addition, differences in side-effect profiles and the duration of treatment may

lead to the choice of either PI for specific patients. Furthermore, the pill burden for patients differs, with boceprevir currently four tablets t.d.s., whereas telaprevir is two tablets t.d.s. It is therefore important that both drugs are available to treating units to enable selection of the most appropriate regimen for individual patients.

(i) Both boceprevir and telaprevir are effective and should be available for use by treating units.

(c) Which regimens to use?

As discussed above, triple therapy regimens with either boceprevir or telaprevir for genotype 1 chronic HCV-infected patients significantly improve SVR rates in both treatment-naïve and experienced patients. Some treatment-naïve patients achieve high SVR rates with SoC treatment alone. Specifically, noncirrhotic genotype 1 patients who have a low baseline viral load (<400 000–800 000 IU/mL) and achieve an RVR (HCV RNA undetectable ($\leq$ 50 IU/mL) at 4 weeks of treatment) with peginterferon-ribavirin are highly likely (80–90%) to achieve an SVR. Indeed, the achievement of an RVR and low basal viral loads are the most significant predictors of achieving an SVR with SoC treatment,[47] and recent guidelines would suggest that treatment duration with peginterferon-ribavirin in these patients could be shortened to 24 weeks.[7] Thus, such good response group patients may not gain much additional benefit in SVR rates from the addition of a PI, but will be exposed to the increased side-effects and risks of resistance. Furthermore, the use of PIs in this group of patients is unlikely to be cost-effective (see above).

As discussed, some of the protease inhibitor clinical trial arms compared response-guided therapy (RGT) with fixed-duration therapy. In treatment-naïve patients, both the SPRINT-2 and ADVANCE studies showed that response-guided therapy had no detrimental effect on overall SVR rate. Furthermore, using RGT in the ADVANCE study enabled reduced treatment duration to 24 weeks in 58% of patients. In addition, the ILLUMINATE study demonstrated that in patients who achieve an eRVR (undetectable HCV RNA at treatment weeks 4 and 12) on telaprevir-based triple therapy, overall treatment can be reduced to 24 weeks with no detrimental effect on SVR rate.[41] In treatment-experienced patients, in the RESPOND study, no statistically significant differences were seen with boceprevir between the RGT arm and the fixed-duration therapy of 48 weeks. However, nonsignificant trends were observed to better SVR rates in the 48 week treatment duration in both prior relapsers and partial responders. In the REALISE study, no RGT arm was included.

The presence of advanced hepatic fibrosis or cirrhosis is a major risk factor for treatment failure. In the PI studies comparing RGT with fixed-duration treatment, the number of patients with cirrhosis is generally small. Furthermore, in these patients, there are nonsignificant trends towards better SVR rates with fixed-duration therapy.[16, 20, 41] Therefore, there is currently insufficient evidence for the use of RGT in cirrhotic patients.

The most difficult to treat group of patients, cirrhotic prior null responders, were only specifically studied in the REALISE trial, with fairly modest numbers.[21] Whilst there was an improved outcome in these patients with telaprevir-based triple therapy compared with SoC, the SVR rate was still only 22–28%. Furthermore, relapse rates were high (25–27%) with even higher levels of virological failure (47–57%), predominantly due to the emergence of resistant variants. Detailed analysis of the lead-in peginterferon-ribavirin T12PR48 group demonstrated that in prior null responders, poor response to lead-in therapy (<1 $\log_{10}$ reduction in HCV RNA at week 4) was also predictive of a poor SVR rate of under 20%.[21] Similarly, in RESPOND-2, a poor response to lead-in peginterferon-ribavirin was associated with low SVR rates in prior partial responders.[20] Therefore, whilst improved over previous therapies, SVR rates are likely to remain low in cirrhotic prior null responders, particularly in the context of a poor response to lead-in peginterferon-ribavirin. Treating these patients with PIs is also likely to increase development of resistance mutants, potentially jeopardising the use of future DAAs. Therefore, careful consideration should be given to the best management option for this group.

(a) **Regimens in treatment-naïve patients (see Figure 1).**

(i) **Either boceprevir or telaprevir can be used** according to the relevant prescribing information.

(ii) **In noncirrhotic treatment-naïve patients with low baseline viral loads (<800 000 IU/mL) and no additional risk factors for treatment failure, who are treated with regimens incorporating a 4 week lead-in with peginterferon-ribavirin and who achieve an RVR following lead-in, consideration can be given to continuing treatment with SoC therapy alone without addition of a PI.** This decision should be made following a balanced discussion with the patient regarding the rates of SVR and the potential side-effects from the addition of a PI.

(iii) **Response-guided therapy with either boceprevir or telaprevir can be used in noncirrhotic treat-**

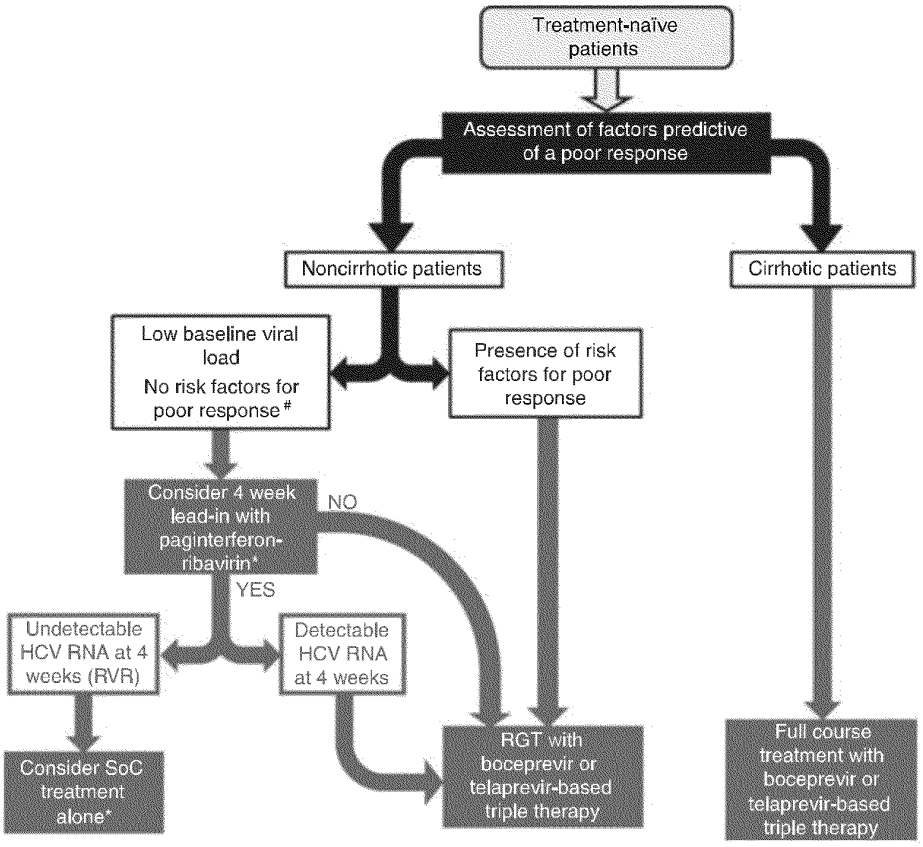

Figure 1 | Proposed algorithm for the use of protease inhibitors in treatment-naïve HCV genotype 1 infected patients. Pre-treatment assessment should include careful consideration of lifestyle factors, co-morbid conditions, potential drug interactions (prescribed and nonprescribed) and assessment for the presence of cirrhosis (by non-invasive or invasive means). In noncirrhotic patients, the presence of factors predictive of a poor response to therapy should be evaluated (#IL-28B genotype; age; ethnic origin; BMI; Type 2 diabetes; HCV genotype 1a vs. 1b). *In noncirrhotic patients with no risk factors for a poor response to therapy, the decision to use a 4-week lead-in with peginterferon and ribavirin and to continue on SoC in those who achieve an RVR should only be taken following careful and balanced discussion with the patient.

ment-naïve patients, enabling reduced treatment duration in a proportion of patients with no adverse effects on SVR. This should be done according to the relevant prescribing information.

(iv) **In cirrhotic treatment-naïve patients, a full 48 week course of treatment,** incorporating 12 weeks of telaprevir or 44 weeks of boceprevir, should be instituted according to the relevant prescribing information

(b) Regimens in patients with previous virological failure (see Figure 2).

(i) **Either boceprevir or telaprevir can be used** according to the relevant prescribing information.

(ii) **Where no data are available on the degree of previous response, patients should be treated with a full treatment course** as per prior null responders to maximise cure rates.

(iii) In patients with factors predicting poor treatment response, who also currently have a low risk of progressive liver disease, before therapy, a discussion should occur to consider watchful waiting as an alternative to PI treatment pending the development of new treatment options.

Stopping rules

(a) **Boceprevir-based regimens:**

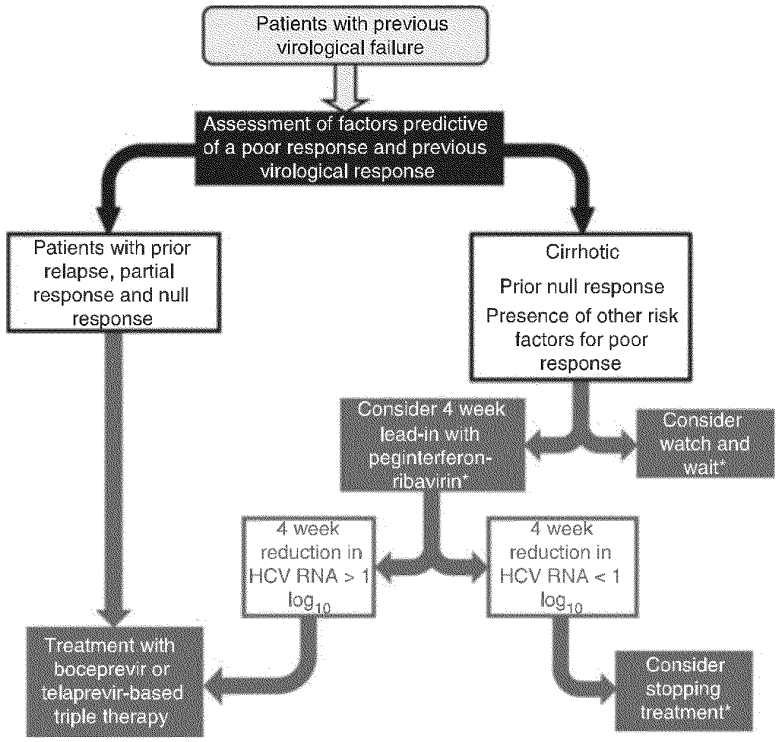

Figure 2 | Proposed algorithm for the use of protease inhibitors in HCV genotype 1 infected patients who have had prior virological failure on treatment. Pre-treatment assessment should include careful consideration of lifestyle factors, co-morbid conditions, potential drug interactions (prescribed and nonprescribed), assessment for the presence of cirrhosis (by non-invasive or invasive means) and the presence of factors predictive of a poor response to therapy. Identification of the degree of previous response should be attempted. If this information is not available, patients should be considered as prior null responders to maximise cure rates. *In cirrhotic prior null responders, the decision to watch and wait for novel therapies or to use a 4-week lead-in with peginterferon and ribavirin to identify patients more likely to achieve an SVR should only be taken following careful and balanced discussion with the patient.

(i) All treatment should be stopped if HCV RNA is >100 IU/mL at treatment week 12 (week 8 of boceprevir) or HCV RNA is detectable at treatment week 24 (week 20 of triple therapy).

(ii) If there is virological breakthrough[4] or incomplete virological response and rebound,[5] treatment with boceprevir should be stopped, but peginterferon-ribavirin may be continued up to 48 weeks at the discretion of the treatment team.

(b) **Telaprevir-based regimens:**

(i) All treatment should be discontinued in patients who have an HCV RNA level >1000 IU/mL after 4 weeks or 12 weeks of triple therapy.

(ii) All treatment should be discontinued if <2 $\log_{10}$ decline from baseline in HCV RNA levels after week 12 of triple therapy

(iii) All treatment should be discontinued if HCV RNA is detectable at any point between treatment week 24 and 44.

(iv) Telaprevir treatment should be stopped if there is virological breakthrough or incomplete virological response and rebound, but peginterferon-ribavirin may be continued at the discretion of the treatment team

(c) **In cirrhotic prior null responders treated with regimens incorporating 4 week lead-in peginterferon-ribavirin, who achieve an HCV RNA reduction of <1**

[4]Virological breakthrough is defined as an achievement of undetectable HCV RNA with subsequent occurrence of HCV RNA >1000 IU/mL.
[5]Incomplete virological response and rebound is defined as an 'on treatment' increase of 1 $\log_{10}$/mL of HCV RNA from the nadir with the HCV RNA level >1000 IU/mL.

$\log_{10}$ IU/mL following lead-in, consideration should be given to stopping treatment. This should be following a balanced discussion with the patient regarding the consequences of a delay in therapy, low SVR rates, high chance of resistance mutations and potential effects this might have on eligibility for next generation treatments (Figure 2).

Management of adverse effects

Common adverse effects such as dysgeusia (boceprevir) and anorectal symptoms (telaprevir) are usually tolerable, do not normally require any treatment and very rarely lead to discontinuation of therapy. The adverse effects requiring intervention are most commonly anaemia, neutropenia and rash.

(a) **Management of anaemia in PI treatment:**

(i) Anaemia (defined as Hb <10 g/dL) in the context of PI treatment should be managed using an escalating combination of:

o Ribavirin dose reduction: it should be started at full treatment dose and dose reduction instituted for anaemia at decrements of 200 mg.
o Reduction in dose of interferon, if bone marrow suppression is evident.
o Erythropoietin administration may be considered and used until Hb > 12 g/dL.
o Supportive treatment with blood transfusion should be considered in extreme circumstances.

(ii) The dose of protease inhibitor should not be reduced for managing anaemia. If required, due to the severity of anaemia, the PI should be stopped completely

(b) **Management of neutropenia.**

(i) Significant neutropenia (absolute neutrophil count <750/mm^3) should be managed according to current practice for SoC treatment. Consideration should be given to dose reduction of Pegylated interferon.

(ii) The dose of protease inhibitor should not be reduced for managing neutropenia or bone marrow suppression. If required due to the severity of neutropenia, the PI should be stopped completely.

(c) **Management of rash** in telaprevir-treated patients.

(i) Rash management plan.

o Mild/moderate: Topical steroids, topical antihistamines, avoidance of sun exposure, wearing loose-fitting clothes. Continue triple therapy.
o Moderate progressive: Stop telaprevir. Monitor for 7 days and consider stopping peginterferon-ribavirin if not improving.
o Severe or SCARs: Stop all treatment. Urgent dermatology review.

FUTURE DEVELOPMENTS

Boceprevir and telaprevir, the first generation of DAAs for HCV to be widely used in clinical practice, represent major progress in management. These drugs are likely to be the first in a long line of DAAs, with newer PIs in addition to polymerase inhibitors, nucleoside analogues and NS5A inhibitors currently under development, with promising early results. Indeed, studies using interferon-free regimes with combinations of new DAAs in small numbers of patients have shown high rates of viral response, even in the difficult to treat groups such as prior null responders.[48–50] These exciting developments highlight the importance of judicious use of boceprevir and telaprevir, closely following the suggested regimens and stopping rules, so as not to negatively influence the possibility of treatment when the next generation of DAAs become available.

CONCLUSIONS

The advent of protease inhibitor-based triple therapy for chronic genotype 1 HCV infection heralds a new era of treatment for these patients. Cure rates are significantly enhanced, and there is now a viable therapeutic option for the large group of patients who previously failed SoC therapy. Clearly, the ongoing development of the second generation PIs and other directly acting antiviral drugs will yield further improvements in the future, but the judicious use of boceprevir and telaprevir in clinical practice will be invaluable for the management of chronic HCV infection in 2012.

ACKNOWLEDGEMENTS

Declaration of personal interests: A. A. has served as a clinical investigator, consultant and/or member of speakers' bureau for companies Johnson and Johnson and MSD. K. A. has served as a clinical investigator, consultant and/or member of speakers' bureau for companies, Janssen, MSD, Gilead, Abbott, Novartis, BMS, Praesido and Astellas, and has received research funding from Gilead, Roche, BMS and MSD. A. B. has served as a clinical investigator, consultant and/or member of speakers' bureau for Roche, MSD, Gilead, BMS, Janssen and Novartis. J. F. D. has served as a clinical investigator, consultant and/or member of speakers' bureau for companies Roche, MSD, Abbott, Janssen and Gilead, and

has received research funding from Schering Plough, Roche, Abbott and MSD. G. R. F has served as a consultant and/or member of speakers' bureau for Roche, Merck, Gilead, BMS, BI, Chugai and Novartis, and has received research funding from Roche and Chugai. A. F has served as a consultant and/or member of speakers' bureau for companies Schering Plough, Janssen, MSD and Gilead. R. F. has served as a clinical investigator, consultant and/or member of speakers' bureau for Janssen, MSD and Roche. P. C. H. has served as a clinical investigator, consultant and/or member of speakers' bureau for Roche, MSD, Schering Plough, BMS, Gilead and Janssen. D. J. M. has served as a consultant to MSD and Janssen. S. D. R has served as a clinical investigator, consultant and/or member of speakers' bureau for Roche, Merck and Janssen, and has received research funding from Roche. *Declaration of funding interests*: None.

REFERENCES

1. Lavanchy D. The global burden of hepatitis C. *Liver Int* 2009; **29**(Suppl. 1): 74–81.
2. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis* 2005; **5**: 558–67.
3. Alter HJ, Seeff LB. Recovery, persistence, and sequelae in hepatitis C virus infection: a perspective on long-term outcome. *Semin Liver Dis* 2000; **20**: 17–35.
4. Camma C, Giunta M, Andreone P, Craxi A. Interferon and prevention of hepatocellular carcinoma in viral cirrhosis: an evidence-based approach. *J Hepatol* 2001; **34**: 593–602.
5. Davis GL, Albright JE, Cook SF, Rosenberg DM. Projecting future complications of chronic hepatitis C in the United States. *Liver Transpl* 2003; **9**: 331–8.
6. Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology* 2010; **138**: 513–21.
7. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol* 2011; **55**: 245–64.
8. Manns MP, McHutchison JG, Gordon SC, *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**: 958–65.
9. Fried MW, Shiffman ML, Reddy KR, *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; **347**: 975–82.
10. McHutchison JG, Lawitz EJ, Shiffman ML, *et al.* Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009; **361**: 580–93.
11. Shiffman ML, Di Bisceglie AM, Lindsay KL, *et al.* Peginterferon alfa-2a and ribavirin in patients with chronic hepatitis C who have failed prior treatment. *Gastroenterology* 2004; **126**: 1015–23.
12. Poynard T, Colombo M, Bruix J, *et al.* Peginterferon alfa-2b and ribavirin: effective in patients with hepatitis C who failed interferon alfa/ribavirin therapy. *Gastroenterology* 2009; **136**: 1618–28.
13. Jensen DM, Marcellin P, Freilich B, *et al.* Re-treatment of patients with chronic hepatitis C who do not respond to peginterferon-alpha2b: a randomized trial. *Ann Intern Med* 2009; **150**: 528–40.
14. Rosen HR. Clinical practice. Chronic hepatitis C infection. *N Engl J Med* 2011; **364**: 2429–38.
15. Kwo PY, Lawitz EJ, McCone J, *et al.* Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. *Lancet* 2010; **376**: 705–16.
16. Poordad F, McCone J Jr, Bacon BR, *et al.* Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364**: 1195–206.
17. McHutchison JG, Everson GT, Gordon SC, *et al.* Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med* 2009; **360**: 1827–38.
18. Hezode C, Forestier N, Dusheiko G, *et al.* Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *N Engl J Med* 2009; **360**: 1839–50.
19. Jacobson IM, McHutchison JG, Dusheiko G, *et al.* Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011; **364**: 2405–16.
20. Bacon BR, Gordon SC, Lawitz E, *et al.* Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364**: 1207–17.
21. Zeuzem S, Andreone P, Pol S, *et al.* Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011; **364**: 2417–28.
22. Foster GR, Hezode C, Bronowicki JP, *et al.* Telaprevir alone or with peginterferon and ribavirin reduces HCV RNA in patients with chronic genotype 2 but not genotype 3 infections. *Gastroenterology* 2011; **141**: 881–9.
23. Mangia A, Mottola L. Treatment of non-genotype 1 hepatitis C virus patients. *Curr Gastroenterol Rep* 2012; **14**: 87–93.
24. Ferrante SA, Chhatwal J, Elbasha E, *et al. Cost-Effectiveness of Boceprevir Based Regimens in Previously Untreated Adult Subjects with Chronic Hepatitis C Genotype 1.* San Francisco: AASLD, 2011.
25. Chhatwal J, Ferrante SA, Dasbach EJ, *et al. Cost-effectiveness of Boceprevir Use in Patients with Chronic Hepatitis C Genotype-1 Who Failed Prior Treatment with Peginterferon/Ribavirin.* San Francisco: AASLD, 2011.
26. Gellad ZF, Naggie S, Reed SD, *et al. The Cost-Effectiveness of a Telaprevir-Inclusive Regimen as Initial Therapy for Genotype 1 Hepatitis C Infection in Individuals with the CC IL-28B Polymorphism.* San Francisco: AASLD, 2011.
27. Kau A, Vermehren J, Sarrazin C. Treatment predictors of a sustained virologic response in hepatitis B and C. *J Hepatol* 2008; **49**: 634–51.
28. Ge D, Fellay J, Thompson AJ, *et al.* Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature* 2009; **461**: 399–401.

29. 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.
30. 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.
31. Kurosaki M, Tanaka Y, Nishida N, *et al.* Pre-treatment prediction of response to pegylated-interferon plus ribavirin for chronic hepatitis C using genetic polymorphism in IL28B and viral factors. *J Hepatol* 2011; **54**: 439–48.
32. Jafferbhoy H, Miller MH, El Wahed Z, Dillon JF. Pre-treatment prediction of response to pegylated-interferon plus ribavarin for chronic hepatitis C using RVR. *J Hepatol* 2011; **55**: 1162–4.
33. Poordad FF. Review article: the role of rapid virological response in determining treatment duration for chronic hepatitis C. *Aliment Pharmacol Ther* 2010; **31**: 1251–67.
34. Zeuzem S, Foster GR, Andreone P, *et al.* Different likelihood of achieving svr on a telaprevir-containing regimen among null responders, partial responders and relapsers irrespective of similar responses after a peginterferon/ribavirin 4-week lead-in phase: realize study subanalysis. *Hepatology* 2011; **54**: 986A–7.
35. Welsch C, Domingues FS, Susser S, *et al.* Molecular basis of telaprevir resistance due to V36 and T54 mutations in the NS3-4A protease of the hepatitis C virus. *Genome Biol* 2008; **9**: R16.
36. Susser S, Welsch C, Wang Y, *et al.* Characterization of resistance to the protease inhibitor boceprevir in hepatitis C virus-infected patients. *Hepatology* 2009; **50**: 1709–18.
37. Forestier N, Reesink HW, Weegink CJ, *et al.* Antiviral activity of telaprevir (VX-950) and peginterferon alfa-2a in patients with hepatitis C. *Hepatology* 2007; **46**: 640–8.
38. Kieffer TL, Sarrazin C, Miller JS, *et al.* Telaprevir and pegylated interferon-alpha-2a inhibit wild-type and resistant genotype 1 hepatitis C virus replication in patients. *Hepatology* 2007; **46**: 631–9.
39. Vierling JM, Ralston R, Lawitz EJ, *et al.* Long-term outcomes following combination treatment with boceprevir plus peg-intron/ribavirin (P/R) in patients with chronic hepatitis c, genotype 1 (Chc-G1). *J Hepatol* 2010; **52**: S470–1.
40. Zeuzem S, Sulkowski MS, Zoulim F, *et al.* Long-term follow-up of patients with chronic hepatitis c treated with telaprevir in combination with peginterferon alfa-2a and ribavirin: interim analysis of the extend study. *Hepatology* 2010; **52**: S436A.
41. Sherman KE, Flamm SL, Afdhal NH, *et al.* Response-guided telaprevir combination treatment for hepatitis C virus infection. *N Engl J Med* 2011; **365**: 1014–24.
42. Roberts SK, Andreone P, Pol S, *et al.* Impact of anemia and ribavirin dose reduction on SVR to a telaprevir-based regimen in patients with HCV genotype 1 and prior peginterferon/ribavirin treatment failure in the phase III REALIZE study. *Hepatology* 2011; **54**: 1007A–8.
43. Naeger LK, Harrington PR. Effect of On-Treatment Undetectable or Detectable/BLOQ HCV RNA MEasurements on SVR Rates in Phase 3 Clinical Trials of Boceprevir and Telaprevir. In: 6th International Workshop on Hepatitis C – Resistance and New Compounds; 2011 24/06/2011; Cambridge, USA; 2011.
44. Goldberg D, Brown G, Hutchinson S, *et al.* Hepatitis C action plan for Scotland: phase II (May 2008–March 2011). *Euro Surveill* 2008; **13**: 211–2.
45. Marcellin P, Forns X, Goeser T, *et al.* Telaprevir is effective given every 8 or 12 hours with ribavirin and peginterferon alfa-2a or -2b to patients with chronic hepatitis C. *Gastroenterology* 2011; **140**: 459–68.
46. Flamm SL, Lawitz EJ, Jacobson IM, *et al.* High sustained virologic response (SVR) among genotype i previous Non-responders and relapsers to peginterferon/ribavirin when re-treated with boceprevir (BOC) plus peginterferon alfa-2A/ribavirin. *Gastroenterology* 2011; **140**: S145.
47. Fried MW, Hadziyannis SJ, Shiffman ML, Messinger D, Zeuzem S. Rapid virological response is the most important predictor of sustained virological response across genotypes in patients with chronic hepatitis C virus infection. *J Hepatol* 2011; **55**: 69–75.
48. Chayama K, Takahashi S, Toyota J, *et al.* Dual therapy with the NS5A inhibitor BMS-790052 and the NS3 protease inhibitor BMS-650032 in HCV genotype 1b-infected null responders. *Hepatology* 2011 [Epub ahead of print].
49. Zeuzem S, Asselah T, Angus P, *et al.* Efficacy of the protease inhibitor BI 201335, polymerase inhibitor BI 207127, and ribavirin in patients with chronic HCV infection. *Gastroenterology* 2011; **141**: 2047–55.
50. Gane EJ, Roberts SK, Stedman CA, *et al.* Oral combination therapy with a nucleoside polymerase inhibitor (RG7128) and danoprevir for chronic hepatitis C genotype 1 infection (INFORM-1): a randomised, double-blind, placebo-controlled, dose-escalation trial. *Lancet* 2010; **376**: 1467–75.