Research Review
PRODUCT REVIEW

Boceprevir (Victrelis®)

About the Reviewer

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This review discusses the evidence in support of the use of boceprevir (Victrelis®) in the treatment of chronic hepatitis C (HCV) genotype 1 infection. Boceprevir is a novel protease inhibitor that has been shown to significantly improve the rate of virological cure when added to the current standard of care, peginterferon alpha and ribavirin combination therapy (PEG-RBV).[1,2]

Since the discovery of HCV more than 20 years ago, it is now widely recognised as a disease of global importance, with an estimated 150 million people currently infected worldwide.[3] As a leading cause of chronic liver disease and liver cancer, HCV is a major global health problem that requires widespread active interventions for its prevention and control,[4] not least because the annual rate of HCV-related mortality has doubled since 1990 and is expected to double again over the current decade.[5-7]

Incidence and prevalence of HCV in New Zealand

According to the World Health Organization, approximately 150 million people have chronic HCV infection and more than 350,000 people die from HCV-related liver disease every year.[3]

Although no concrete data are available on the prevalence of HCV infection in New Zealand, the Ministry of Health estimates that more than 50,000 of the population are infected.[8] This equates to a prevalence of approximately 1.5% of New Zealanders aged 15 years and over compared with about 2% of the general population worldwide, although considerable variability in the prevalence of HCV exists between countries, with higher rates in the Middle East, Asia and Eastern Europe compared with North/Western Europe, North and South America, and Australasia.[3,4]

The incident rate of reported acute cases of HCV in New Zealand was 0.6 per 100,000 in 2011 (27 cases).[9] However, as acute infection is asymptomatic in most cases (60-70%),[4] this figure is well below the true rate of new cases of HCV infection. Currently, only 25% of New Zealanders infected with HCV are thought to have been diagnosed.[10]

HCV transmission is parenteral. Although the risk of infection through blood transfusion was previously as high as 5% per unit of blood, transfusion-acquired HCV infection was eradicated in New Zealand in 1992 by the introduction of universal testing of blood donors. No cases have been notified since then, despite over two million blood units having been transfused. Nosocomial infection may still occur in developing countries where high-risk practices persist, including paid blood and organ donors, reusable needles and glass syringes. In most developed countries, including New Zealand, HCV infection is now mostly spread through sharing contaminated needles and other equipment during recreational intravenous drug abuse.[11-13] In 2004, the New Zealand National Needle Exchange Blood-borne Virus Seroprevalence Survey found the prevalence of HCV infection among injecting drug users to be 70% and strongly associated with age and duration of injecting.[13] This accounts for an estimated 1200 new infections per annum. In 2002, the Ministry of Health commissioned a National Action Plan for HCV prevention.[14] Although no vaccine is available, this plan identified education of at-risk youth, and introduction of harm reduction strategies (e.g., needle exchange services, safe injecting practices) as high priorities for the control of HCV. Since then, the incidence of HCV infection has almost halved. Less common routes of infection include occupational sharps' injuries, poorly sterilised equipment used for tattooing and body piercing, and mother-to-infant transmission (from HCV+ mother). Sexual HCV transmission is rare in the absence of risk factors associated with increased risk (e.g., HIV co-infection, and sexual practices with increased risk of blood-to-blood exposure such as during menstruation or in the presence of genital ulcers).[13]

Six different genotypes of HCV (1 to 6) have been described and various subtypes. Of these, genotype 1 – primarily subtypes 1a and 1b – is by far the most prevalent worldwide.[12,15,16] HCV genotype distribution has been shown to be associated with age and mode of transmission. Subtype 1b is the phylogenetically oldest subtype, associated with blood transfusions and unsafe medical procedures in Europe.[12] Genotypes 1a and 3a are more recent genotypes associated with injecting drug use in North America and Australasia, and probably originated in South-East Asia. Genotype 4 is found predominantly in the Middle East, genotype 5 in South Africa and genotype 6 in South-East Asia.[15,17] The clinical importance of genotype identification is highlighted by data that show genotype 1 is more resistant to the current standard of care, PEG-RBV, than genotypes 2 and 3, which has implications for the duration of antiviral treatment.[17,18] In addition, subtype 1a is associated with more rapid treatment failure of both interferon-based and interferon-free regimens containing protease inhibitors, NS5A inhibitors and non-nucleoside inhibitors, due to more rapid selection of resistant mutants.[19,20]

Diagnosis

Diagnosis of HCV infection is confirmed by the presence of both HCV RNA, detected by molecular assays, and anti-HCV antibodies, detected by enzyme immunoassays.[16] During acute infection, HCV RNA may be detected within 1 to 3 weeks after viral exposure; seroconversion may occur after 4 to 10 weeks.[21] Symptoms, if they occur, may develop 6 to 8 weeks after exposure and resemble other forms of acute viral hepatitis, including fever, fatigue, nausea, abdominal pain and jaundice.[22] Many patients develop only non-specific symptoms which may further contribute to a lack of diagnosis during the acute phase; jaundice occurs in only 20-30% of cases.[23] Other criteria that may aid diagnosis of acute infection include elevated liver enzymes (≥10-20 times the upper limit of normal), known or

suspected exposure to HCV, and increasing numbers of reactive proteins upon repeated recombinant immunoblot assay testing.[21]

The presence of HCV RNA 6 months after acute infection is a sign of chronic HCV infection; furthermore, anti-HCV antibodies persist for life in patients who develop chronic HCV infection. Aside from diagnosis, HCV RNA testing is used in clinical practice to identify patients in need of antiviral therapy and to monitor the response to treatment.[24]

HCV genotype identification is required prior to initiation of PEG-RBV combination therapy for chronic disease, in order to determine the dose of ribavirin and the duration of treatment required. HCV genotype and subtype may be determined by a number of methods (e.g., direct sequence analysis, reverse hybridization, and genotype-specific real-time PCR), with commercially available assays able to accurately identify the six genotypes, and some also the subtype.[24]

Burden of disease

In general, the majority (60-80%) of patients with acute HCV fail to spontaneously clear the infection, resulting in chronic disease.[16,21,22,25] Spontaneous resolution appears to be associated with the presence of symptoms and a strong cellular immune response.[21]

Chronic infection rarely resolves spontaneously, and is associated with long-term progressive hepatic inflammation and fibrosis of variable degrees, irrespective of HCV genotype and viral load. Factors associated with more rapid liver disease progression include older age at initial infection, male gender, heavy alcohol consumption, heavy cannabis use, diabetes mellitus and obesity, and co-infection with human immunodeficiency virus (HIV).[16,18,26,27] Complications of chronic liver disease may occur 20 to 30 years after onset of HCV infection: 10-20% of cases develop cirrhosis and 1-5% develop liver cancer.[4,28] In fact, HCV is the leading cause of both chronic liver disease and hepatocellular carcinoma (HCC) in industrialised nations.[17,29] It is estimated that the number of new cases of HCV-related hepatocellular carcinoma will double by 2020.[5-7]

Asymptomatic (compensated) cirrhosis may exist for many years prior to the onset of overt liver failure (decompensation), the latter associated with symptoms such as ascites, portosystemic encephalopathy, gastrointestinal bleeding (due to variceal haemorrhage), and hepatorenal syndrome. The annual death rate among patients with decompensated cirrhosis has been estimated at 15% for industrialised countries.[30]

HCC is usually a result of liver cirrhosis and approximately 4% of HCV-positive patients with cirrhosis progress to HCC per year.[28] Worldwide, HCC is the sixth most common cancer but the third most common cause of cancer death. Risk of HCC is higher in men than women, with age-standardised incidence rates in Australia/New Zealand of 5 per 100,000 in men and 2 per 100,000 in women (2008 data).[31] In industrialised countries, with the exception of Japan, the annual death rate in patients with HCC is estimated at 80%.[30]

HCV-associated liver failure and HCC are leading indications for liver transplantation. However, recurrent HCV infection of the allograft is universal and immediate after transplantation and associated with more rapid progression to cirrhosis (20-40% within 5 years).[5]

Extrahepatic manifestations commonly occur at some stage during the course of chronic HCV infection and may be the first signal of disease in asymptomatic individuals.[32] These include cryoglobulinaemia, lichen planus, porphyria cutanea tarda, and glomerulonephritis. There is an also association between non-Hodgkin's lymphoma and HCV infection.[33]

The primary goal of antiviral therapy is to cure the infection. Due to the slow evolution of the disease over several decades, surrogate virological parameters are used to define treatment response rather than a clinical measure. A "virological cure" is known as a sustained virologic response (SVR), commonly defined as an undetectable HCV RNA level (<50 IU/ml) 24 weeks after treatment cessation.[34] However, a 2011 review of more than 10,000 patients treated for chronic HCV across fifteen clinical trials demonstrated almost 100% concordance between undetectability of serum HCV RNA at 12 weeks and at 24 weeks post treatment[35] – i.e., virologic relapse later than 12 weeks post treatment is extremely rare. As a result, the US Food and Drug Administration changed the primary efficacy endpoint for future trials of HCV therapy to SVR at 12 weeks.[36]

The long-term benefits of SVR include reduction in risk of hepatocellular carcinoma and mortality.[37,38] In addition, quality of life and extrahepatic manifestations, such as cryoglobulinaemia, porphyria cutanea tarda, non-Hodgkin's lymphoma, and membranoproliferative glomerulonephritis, all improve following successful treatment.[32,33,39]

An SVR is also associated with resolution of liver disease in patients without cirrhosis; however, those with cirrhosis remain at risk of life-threatening complications. The current standard of care, PEG-RBV combination therapy, has been shown to achieve SVR rates of 40-50% in patients with HCV genotype 1, compared with ≥80% with genotypes 2, 3, 5 and 6.[16] Patients with genotype 4 may respond to treatment at a rate similar or slightly higher rate than those with genotype 1.[40]

Boceprevir: a novel antiviral for HCV

Boceprevir is a direct-acting antiviral treatment for chronic HCV infection. As a novel ketoamide linear protease inhibitor, boceprevir inhibits viral replication by binding covalently but reversibly to the active site of the HCV non-structural protein 3 (NS3) protease. NS3 is an essential virally-encoded enzyme that cleaves the HCV polyprotein at specific sites to form the functional proteins required for viral replication. Boceprevir has demonstrated potent *in vitro* antiviral activity against HCV genotypes 1a and 1b. Like other protease inhibitors, boceprevir is given with PEG-RBV to minimise the emergence of viral resistance. In replicon studies, the addition of boceprevir to interferon produced additive antiviral effect with no evidence of synergism or antagonism.[41]

Pharmacokinetics of boceprevir

The approved dosage of boceprevir is 800 mg three times daily (TID). Following oral administration of boceprevir, T_{max} occurs after a median of 2 hours. In pharmacokinetic studies, steady-state AUC, C_{max} and C_{min} increased in a less than dose-proportional manner and individual exposures overlapped substantially at 800 mg and 1,200 mg, suggesting diminished absorption at higher doses. Accumulation is minimal and pharmacokinetic steady state is achieved after approximately 1 day with TID dosing. Food enhanced the exposure of boceprevir by up to 60% at a dose of 800 mg TID when administered with a meal relative to the fasting state. The bioavailability of boceprevir was similar regardless of meal type (e.g., high-fat vs. low-fat) or whether taken 5 minutes prior to eating, during a meal, or immediately following completion of the meal. Based on these findings, boceprevir was dosed with food in Phase 2 and Phase 3 studies.[41]

Boceprevir is not highly bound to human plasma proteins (~75% following a single dose of boceprevir 800 mg). Metabolism is primarily through the aldoketoreductase (AKR)-mediated pathway to ketone-reduced metabolites that are inactive against HCV; to a lesser extent, boceprevir also undergoes oxidative metabolism mediated by CYP3A4/5. Boceprevir is eliminated with a mean plasma half-life of approximately 3.4 hours, primarily via the liver through the faeces. No clinically significant differences in pharmacokinetic parameters were observed in studies of patients with end-stage renal disease and varying degrees of stable chronic liver impairment – no dosage adjustment of boceprevir is therefore required in these subgroups.[41]

Safety profile

In an integrated analysis of Phase 2 and 3 clinical trials, boceprevir plus PEG-RBV triple therapy was associated with a similar rate of treatment-related adverse events, serious adverse events and discontinuations due to adverse events compared with control (PEG-RBV dual therapy). The most commonly reported treatment-related adverse events (≥10% incidence) were fatigue, anaemia, nausea, headache, and dysgeusia (change in the sense of taste), reported in >35% of patients. Anaemia (49% vs. 29%) and dysgeusia (37% vs. 15%) were the only two events that were reported with a ≥10% difference in the combined boceprevir plus PEG-RBV triple therapy arms compared with the combined PEG-RBV dual therapy control arms. Serious adverse events were reported in 11% and 8% of patients respectively; deaths occurred in <1% and 1%, respectively. Discontinuation due to adverse events occurred in 13% of patients treated with boceprevir plus PEG-RBV and 12% treated with PEG-RBV alone; most frequent causes were fatigue (2% vs. 3%) and anaemia (1% each). Dose modifications of any medication due to adverse events were reported in 39% and 24% of patients, respectively, mostly for anaemia or neutropenia and overwhelmingly made for PEG-RBV. Anaemia was managed primarily with ribavirin dose reduction and/or erythropoietin use; 3% of patients receiving boceprevir plus PEG-RBV received a blood transfusion versus <1% with PEG-RBV alone.[41]

Clinical efficacy

During clinical development, boceprevir was studied in combination with the current standard of care (PEG-RBV) in 1,500 adult patients with chronic HCV genotype 1 infection in two pivotal, international, randomised, double-blind, placebo-controlled Phase 3 trials: the SPRINT-2 study recruited previously untreated patients and the RESPOND-2 study recruited patients who had failed previous therapy.[1,2]

Results of a prior Phase 2 dose-finding study in treatment-failure patients (RESPOND-1) suggested that the optimal dose of boceprevir is 800 mg TID; the data also supported further evaluation of a 36-week treatment period in patients with an early virologic response as well as the use of a 4-week lead-in period with PEG-RBV before the addition of boceprevir. This approach ensures that ribavirin steady state concentration is reached and interferon activity is fully realised at the point of boceprevir introduction, thereby avoiding functional monotherapy and potentially already reducing the overall viral load. It is thought this may reduce the likelihood of the emergence of resistance to boceprevir and also limits boceprevir treatment to patients who are able to tolerate the first 4 weeks of PEG-RBV dual therapy.[41]

A second Phase 2 study in treatment-naïve patients (SPRINT-1) also supported the utility of a 4-week PEG-RBV lead-in period, as well as the need for full-dose ribavirin therapy. Furthermore, bi-weekly assessments of HCV-RNA suggested that 28 weeks of treatment were as effective as 48 weeks of treatment in patients whose first undetectable HCV-RNA result occurred at or before week 8 of treatment (early responders), i.e., after 4 weeks of boceprevir. Conversely, longer treatment duration only improved SVR in patients whose first undetectable HCV-RNA result occurred after 8 weeks (late responders).[41]

In the Phase 3 SPRINT-2 study in treatment-naïve patients (n=1,097) with chronic HCV genotype 1, 48 weeks of PEG-RBV dual therapy (control arm) was compared with two treatment regimens containing boceprevir 800 mg TID: response-guided therapy consisting of 24 weeks of triple therapy in early responders and 24 weeks of triple therapy plus 20 additional weeks of PEG-RBV dual therapy in late responders; and fixed-duration therapy consisting of triple therapy for 44 weeks. PEG-RBV was administered in both boceprevir arms for 4 weeks prior to the addition of boceprevir. In all arms, patients with detectable HCV RNA at week 24 discontinued all treatment for futility. Because of the marked differences in response rates with PEG-RBV between black and non-black patients, patients were enrolled into two cohorts based on self-identified race. The primary endpoint of a sustained virologic response (SVR), defined as undetectable HCV RNA levels for 24 weeks after the completion of therapy (week 72), was achieved in 63% who received response-guided triple therapy and in 66% who received fixed-duration triple therapy, versus 38% with control ($p<0.0001$ for both comparisons). In the cohort of black patients (n=159), the respective rates of SVR were 42% and 53% versus 23% ($p=0.044$ and $p=0.004$, respectively); in non-blacks (n=938) the respective rates of SVR were 67% and 68% versus 40% ($p<0.0001$ for both comparisons). Thus, the addition of boceprevir to the standard of care was shown to significantly improve virological cure in treatment-naïve patients as part of either a response-guided or fixed-duration regimen and irrespective of race (black or non-black).[1,41]

The Phase 3 RESPOND-2 study in patients (n=403) who had failed previous therapy was similarly designed, except that response-guided therapy consisted of 36 weeks of triple therapy in early responders and 36 weeks of triple therapy plus 12 additional weeks of PEG-RBV dual therapy in late responders; in addition, treatment cessation for futility occurred at week 12. Eligible patients were enrolled following a qualifying (previous) treatment regimen of PEG-RBV if they had demonstrated responsiveness to at least 12 weeks of therapy but had failed to achieve SVR. At week 72, 59% of patients who received response-guided triple therapy and 66% who received fixed-duration triple therapy achieved SVR, versus 21% with control ($p<0.0001$ for both comparisons). As with SPRINT-2, the addition of boceprevir to the standard of care was shown to significantly improve virological cure, this time in failed patients, as part of either a response-guided or fixed-duration regimen.[2,41]

In both treatment-naïve and treatment-experienced patients, therefore, the addition of boceprevir to the standard of care was shown to be an effective treatment that significantly increases SVR rates, including in sub-populations, and offers shorter therapy for many patients that achieve an early response. Several large, post-approval studies are currently in progress.

Resistance

In the Phase 3 studies, an as-treated, pooled genotypic resistance analysis was conducted in patients receiving boceprevir plus PEG-RBV. Among boceprevir-treated patients who did not achieve SVR, and for whom samples were analyzed, 53% had one or more specific post-baseline, treatment-emergent NS3 protease domain amino acid substitutions detected by a population-based sequencing assay. Nearly all of these substitutions have been shown to reduce boceprevir anti-HCV activity in cell culture or biochemical assays. However, these resistance-associated variants (RAVs) were detected in a small proportion of patients prior to treatment, and due to the high SVR rates in boceprevir-treated patients, their emergence was infrequent. Responsiveness to interferon (≥1-$\log_{10}$ decline in viral load at the end of the 4-week PEG-RBV lead-in period) was associated with a reduced emergence of boceprevir RAVs, but clear patterns of substitutions were not observed. Of note, after treatment cessation the number of RAVs declined over time, and different RAVs declined at different rates, likely reflecting differing effects on viral fitness.[41,42] Following protease inhibitor treatment failure, RAVs persisted longer in patients infected with HCV subtype 1a than in those infected with subtype 1b.[43]

Indication and availability

In New Zealand, boceprevir (VICTRELIS®) is approved for the treatment of chronic HCV genotype 1 infection, in a combination regimen with PEG-RBV, in adult patients (18 years and older) with compensated liver disease who are previously untreated or who have failed therapy.[42] VICTRELIS® is a fully funded medicine. Special Authority Criteria apply. For more information visit the Pharmac website www.pharmac.govt.nz

EFFICACY AND SAFETY OF BOCEPREVIR IN MAJOR CLINICAL TRIALS IN CHRONIC HCV GENOTYPE 1 INFECTION

Boceprevir for untreated chronic HCV genotype 1 infection[1]

Authors: Poordad F, et al.

Summary: Adults with previously untreated chronic HCV genotype 1 infection (n=1097) were randomised to one of three groups. All patients received PEG-RBV for 4 weeks during a lead-in period. Subsequently, group 1 (control group) received placebo plus PEG-RBV for 44 weeks; group 2 received boceprevir plus PEG-RBV for 24 weeks, and those with detectable HCV RNA at week 8 received placebo plus PEG-RBV for an additional 20 weeks; and group 3 received boceprevir plus PEG-RBV for 44 weeks. Non-black (n=938) and black (n=159) patients were enrolled and analysed separately. A sustained virologic response (SVR), defined as an undetectable HCV RNA 24 weeks post treatment, occurred in 40% in group 1 (control), 67% in group 2 ($p<0.001$), and 68% in group 3 ($p<0.001$) in the non-black cohort, and in 23%, 42% ($p=0.04$) and 53% ($p=0.004$), respectively in the black cohort. In group 2, 44% of patients had undetectable HCV RNA at week 8 and received a total of 28 weeks of treatment. Anaemia led to dose reductions in 21% of boceprevir-treated patients versus 13% with control; discontinuations for anaemia occurred in 2% and 1%, respectively. In conclusion, the addition of boceprevir to PEG-RBV significantly increased the rates of SVR in previously untreated patients with chronic HCV genotype 1 infection compared with PEG-RBV alone. The rates were similar with 24 and 44 weeks of boceprevir treatment.

Comment: SPRINT-2 is the Phase III registration study of the first-generation protease inhibitor boceprevir (BOC) for treatment-naïve HCV genotype 1 infection. The addition of BOC to PEG/RBV increased the SVR rate from 40% to 67% in non-blacks. One arm of the study was a response-guided therapy (RGT) arm, whereby patients with undetectable HCV RNA between weeks 8 and 24 received only 24 weeks of BOC/PEG/RBV whilst the rest received 24 weeks of BOC/PEG/RBV followed by an additional 20 weeks of PEG/RBV. Most treatment-naïve patients in the RGT arm were able to be treated with the shorter duration.

This study further confirmed the utility of the 4-week lead-in approach, which determines the IFN-responsiveness of the patient's HCV. This "lead-in" should help prevent the emergence of BOC-resistant mutants and is recommended on the label (note that telaprevir regimens do not include a PEG/RBV lead-in phase). Also, this lead-in allowed the investigators to study the effect of IFN-responsiveness on SVR among patients treated with BOC/PEG-RBV. Only 29% of patients who had a <1 $\log_{10}$ drop in HCV RNA after the lead-in period achieved SVR compared to 82% of those who achieved an initial 1 $\log_{10}$ drop. At this time, however, there is no strong recommendation to stop treatment in those who fail to achieve a 1 $\log_{10}$ drop in HCV RNA during the lead-in phase. The increased treatment failure rate in patients who failed to achieve an initial 1 $\log_{10}$ reduction is due to an increased rate of BOC resistance – 52% compared to only 4% in those patients with at least a 1 $\log_{10}$ reduction after lead-in.

The excellent results of SPRINT-II have led to the regulatory approval of boceprevir in the USA (FDA, May 2011) and Europe (EMA, August 2011) for treatment-naïve HCV genotype 1 infection and BOC/PEG/RBV has become the new "standard-of-care" for treatment-naïve genotype 1 HCV. Boceprevir has been recently approved in Australia and here in New Zealand and a decision on funding is awaited.

Boceprevir for previously treated chronic HCV genotype 1 infection[2]

Authors: Bacon BR, et al.

Summary: Adults with chronic HCV genotype 1 infection and without a sustained response to PEG-RBV therapy (n=403) were randomised to one of three groups. All patients received PEG-RBV for 4 weeks during a lead-in period. Subsequently, group 1 (control group) received placebo plus PEG-RBV for 44 weeks; group 2 received boceprevir plus PEG-RBV for 32 weeks, and those with detectable HCV RNA at week 8 received placebo plus PEG-RBV for an additional 12 weeks; and group 3 received boceprevir plus PEG-RBV for 44 weeks. The rate of sustained virologic response (SVR), defined as undetectable HCV RNA 24 weeks post treatment, was significantly higher in the two boceprevir groups (group 2, 59%; group 3, 66%; vs. control, 21%, p<0.001). The rate of SVR in patients with undetectable HCV RNA at week 8 was 86% and 88% after 32 weeks and 44 weeks of triple therapy, respectively. Among patients with a decrease in HCV RNA <1 $\log_{10}$ IU/ml after the lead-in period (week 4), rates of SVR were 0%, 33% and 34% in groups 1, 2, and 3, respectively. Anaemia occurred significantly more often in the boceprevir groups than with control; erythropoietin was administered in 41-46% of boceprevir-treated patients and in 21% of controls. In conclusion, the addition of boceprevir to PEG-RBV resulted in significantly higher rates of SVR in previously treated patients with chronic HCV genotype 1 infection compared with PEG-RBV alone.

Comment RESPOND-2 is a Phase III registration study of boceprevir (BOC) for treatment-experienced HCV genotype 1 infection. The addition of BOC to PEG/RBV increased the SVR rate from 21% to 66%. SVR rates were higher in previous responder-relapsers (75%) than in prior partial responders (52%). Null responders were not included in this study but were included in the separate "Provide Study" (see below). As with the treatment-naïve study, the response-guided therapy (RGT) approach was evaluated. In the RGT arm, rapid responders (defined as undetectable HCV RNA between weeks 8 and 24) received only 32 weeks of BOC/PEG/RBV whilst the rest received 32 weeks of BOC/PEG/RBV followed by and additional 12 weeks PEG/RBV. This RGT approach was justified for noncirrhotic but not for cirrhotic treatment-experienced patients, where the SVR achieved with the shortened duration was almost 20% lower than that for fixed longer duration.

As with the treatment-naïve study, the 4-week lead-in phase with PEG/RBV was used in all patients receiving BOC and has been included in the registration label. The SVR rate was lower in those patients who failed to achieve a 1 $\log_{10}$ decline in HCV RNA during the lead-in phase: 33% vs. 79%.

As in SPRINT-2, anaemia is the most frequent adverse effect of BOC-based triple therapy in treatment-experienced patients. Abnormal taste (disguesia) was also a common symptom during BOC therapy.

Factors that predict response of patients with hepatitis C virus infection to boceprevir[45]

Authors: Poordad F, et al.

Summary: The authors of this study used multivariate regression analysis to identify baseline host factors, including interleukin (IL)-28B polymorphisms, associated with a sustained virologic response (SVR) to boceprevir plus PEG-RBV treatment (28 to 48 weeks) in patients with chronic HCV infection in two pivotal Phase 3 trials: SPRINT-2 in previously untreated patients; and RESPOND-2 in patients who did not respond to prior therapy. In SPRINT-2, SVR was predicted by low viral load (odds ratio [OR], 11.6), IL-28B genotype (rs 12979860 CC vs. TT and CT; ORs, 2.6 and 2.1, respectively), absence of cirrhosis (OR, 4.3), HCV subtype 1b (OR, 2.0), and non-black race (OR, 2.0). In RESPOND-2, SVR was predicted only by previous relapse, compared with previous non-response (OR, 2.6). The majority of patients (76-89%) with IL-28B genotype rs 12979860 CC had undetectable levels of HCV RNA after 8 weeks of treatment (4 weeks of PEG-RBV [lead-in] and 4 weeks of boceprevir plus PEG-RBV) and were eligible for shortened therapy (28 weeks). In both studies, IL-28B rs12979860 CC was associated more strongly with a good response to interferon (≥1 $\log_{10}$ decrease in HCV RNA) after 4 weeks of lead-in treatment than other baseline factors; however, a good response to interferon at week 4 was associated more strongly with SVR than IL-28B rs12979860. In conclusion, IL-28B genotype rs 12979860 CC is associated with response to boceprevir plus PEG-RBV and can identify candidates for shortened therapy. However, a good response to interferon lead-in treatment (≥1 $\log_{10}$ decrease in HCV RNA at week 4 week) is the strongest predictor of a SVR, regardless of polymorphisms in IL-28B.

Comment: Host IL-28B genotype was a baseline predictor of response in SPRINT-2. In the standard-of-care PEG-RBV arm, SVR rates were 78% in patients with IL-28B CC genotype, 28% in CT and 27% in TT. In the boceprevir response-guided therapy (RGT) arm, SVR rates were 82% in patients with IL-28B CC genotype, 65% in CT and 55% in TT. Therefore, the addition of boceprevir did not significantly improve SVR rates in CC patents (although more patients were able to shorten duration of therapy in the RGT arm). Baseline predictors of response in RESPOND-2 included host IL-28B genotype and previous response to PEG-RBV. In the standard-of-care PEG-RBV arm, SVR rates were 46% in patients with IL-28B CC genotype, 17% in CT and 50% in TT. In the boceprevir RGT arm, SVR rates were 79% in patients with IL-28B CC genotype, 61% in CT and 55% in TT. Therefore, unlike the SPRINT-2 study, the addition of boceprevir did significantly improve SVR rates in CC patents (although these made up only 20% of nonresponders in this study). The overall rate of SVR was 69% in previous responder-relapsers and 40% in partial responders. No null responders were included in this study.

Sustained virologic response (SVR) in prior peginterferon/ribavirin (PR) treatment failures after retreatment with boceprevir (BOC) + PR: the PROVIDE study interim results[46]

Authors: Bronowicki J, et al.

Summary: Chronically infected HCV patients in the PEG-RBV control arms of boceprevir Phase 2/3 studies who did not achieve a sustained virologic response (SVR), defined as undetectable HCV RNA 24 weeks post treatment, were eligible to enrol in the PROVIDE study and receive treatment with boceprevir (800 mg TID with food) plus PEG-RBV (peginterferon 1.5 µg/kg/week and weight-based ribavirin [600-1400 mg/day]) for up to 44 weeks. If >2 weeks had elapsed since the end of PEG-RBV treatment in the previous study, PEG-RBV was given for 4 weeks (lead-in) prior to the addition of boceprevir. The authors presented an interim analysis of data from 163 patients. SVR was reported in 40% of prior null responders (<2 $\log_{10}$ decline in HCV RNA at week 12 in prior study) and in 68% of prior partial responders/relapsers. After the PEG-RBV lead-in, 78% of prior null responders and 24% of prior partial responders/relapsers had a <1 $\log_{10}$ decline in HCV RNA. Overall, SVR rates were 47% and 68% in patients with a <1 $\log_{10}$ decline and a ≥1 $\log_{10}$ decline in HCV RNA after lead-in, respectively. Anaemia occurred in 48%, dysgeusia in 34% and neutropenia in 22%; 7% discontinued due to adverse events. In conclusion, boceprevir plus PEG-RBV achieved high SVR rates, irrespective of prior response to PEG-RBV. Responsiveness to interferon after PEG-RBV lead-in correlates with prior response and may predict SVR in prior null responders.

Comment: This small, uncontrolled study was conducted in null responders and partial responders. Response-guided therapy was not implemented in this study with all patients treated for 44 weeks with boceprevir (BOC) after 4 weeks of PEG-RBV lead-in. As in RESPOND-2, SVR rate was determined by previous treatment response to prior PEG/RBV. This again emphasises the importance of interferon responsiveness to the efficacy of BOC/PEG/RBV triple therapy. Although patients who experienced favourable response to the 4-week PEG/RBV lead-in did have a higher SVR rate (Δ 21%), this difference was not as great as observed in the SPRINT-2 study (Δ 53%), reflecting the enrichment of null responder studies with patients with reduced IFN responsiveness. Despite the author's conclusion, even without a 1 $\log_{10}$ reduction in HCV RNA during the PEG/RBV lead-in almost 50% subsequently achieved SVR. This observation would argue against using a <1 $\log_{10}$ reduction in HCV RNA during lead-in as a stand-alone futility rule to stop treatment for non-response.

The interim results from this study would strongly support the use of BOC/PEG/RBV in HCV genotype 1 prior nonresponders including null responders.

A randomized trial comparing ribavirin dose reduction versus erythropoietin for anemia management in previously untreated patients with chronic hepatitis C receiving boceprevir plus peginterferon/ribavirin[47]

Authors: Poordad F, et al.

Summary: Treatment-naïve chronic HCV genotype 1 adults (n=687) with baseline haemoglobin (Hb) 12-15 g/dl in women and 13-15 g/dl men received open-label PEG-RBV (600-1400 mg/day) for 4 weeks then boceprevir (800 mg TID) plus PEG-RBV for 24 or 44 weeks, depending on HCV-RNA level after 8 weeks of treatment. A total of 500 patients developed anaemia (Hb ≤10 g/dl or expected to reach that nadir before the next visit) and were randomised to receive either RBV dose reduction (DR) by 200-400 mg/day or erythropoietin (EPO) 40,000 units/wk subcutaneously. Secondary management strategies such as EPO, RBV DR, or transfusion in patients with Hb ≤8.5 g/dl could be used by investigators to prevent study discontinuation. The primary endpoint of sustained virologic response (SVR), defined as undetectable HCV RNA 24 weeks post treatment, was comparable between the two arms (RBV DR 71.5% vs. EPO 70.9%), as was the relapse rate (9.7% vs. 9.6%). Multivariate logistic regression analyses found no significant between-group differences for subgroups including gender, age, fibrosis score, baseline Hb, and time to anaemia onset. No secondary anaemia intervention was required in 82% in the RBV DR arm and 62% receiving EPO. Serious adverse events occurred in 16% and 13% of the RBV DR and EPO arms, respectively. Discontinuation for any adverse event (11% and 13%, respectively) and due to anaemia (2.0% and 2.4%, respectively) was similar in the two arms. Rates of other adverse events were comparable. In conclusion, the rate of SVR was approximately 71% in anaemia patients treated with boceprevir plus PEG-RBV; the results of the present study support RBV dose reduction for primary anaemia management. The safety profiles of the two anaemia management strategies were similar.

Comment: Ribavirin causes anaemia through accumulation within red blood cell membranes, thereby increasing red blood cell fragility and subsequent haemolysis. In a previous review of studies of PEG/RBV, Shiffman concluded that RBV-dose reduction for anaemia did not adversely impact on SVR rates.[48] It can be assumed that anaemia was a surrogate marker of increased RBV exposure – the worse the anaemia, likely the higher the RBV levels within the hepatocyte and the increased antiviral effect of this agent.

In this prospective study, patients with Hb <10 g/dl who were randomised to RBV dose reduction had the same SVR rates as those who received erythropoietin. Twice as many randomised to erythropoietin required an additional strategy because of intractable anaemia. The cost savings associated with RBV dose-reduction strategy will be considerable.

Based on these observations and those of Shiffman,[48] the preferred management strategy for anaemia during boceprevir-based triple therapy is reduction of ribavirin dose rather than erythropoietin or blood transfusion.

Adherence to assigned dosing regimen and sustained virologic response among hepatitis C-genotype 1 previously untreated and peginterferon/ribavirin treatment-failure patients treated with boceprevir plus peginterferon alfa-2b/ribavirin[49]

Authors: Gordon SC, et al.

Summary: The authors examined the relationship between adherence to antiviral triple therapy dosage and duration and sustained virologic response (SVR) in treatment-naïve and prior treatment-failed chronic HCV patients who took part in the pivotal Phase 3 studies SPRINT-2 and RESPOND-2, respectively. Patients received PEG-RBV dual therapy for 44 weeks or boceprevir (800 mg TID) plus PEG-RBV triple therapy for 24 to 44 weeks, depending on prior treatment status and on-therapy treatment response, preceded by 4 weeks of PEG-RBV. Across the two studies, 89-91% of patients reported ≥80% adherence to assigned triple therapy duration and dosing. Assigned treatment duration adherence of ≥80% was the most important factor in achieving a high SVR (83-85%), even in patients with <80% adherence to boceprevir dose. In conclusion, boceprevir TID dosing was effective, and strict adherence to the 7-9-hour boceprevir dosing interval had minimal impact on SVR in patients otherwise adherent to therapy.

Comment: This retrospective analysis of the SPRINT-2 and RESPOND-2 results confirm the importance of adherence to both PEG and RBV in achieving SVR on boceprevir-based triple therapy. The reported 90% adherence rate is excellent but will in part reflect the close supervisions associated with participation in a clinical trial. Therefore it will be important to assess adherence in the "real world" because reduced adherence to PEG/RBV will likely result in increased treatment failure due to emergence of boceprevir resistance.

Safety of telaprevir or boceprevir in combination with peginterferon alfa/ribavirin, in cirrhotic non responders. First results of the French Early Access Program (ANRS CO20-CUPIC)[50]

Authors: Hezode C, et al.

Summary: Few cirrhotic patients were included in Phase 3 trials of boceprevir and telaprevir. The authors presented safety data on the use of boceprevir and telaprevir, in combination with PEG-RBV, in patients with compensated cirrhosis (Child-Pugh class A), HCV genotype 1 infection and prior relapse or partial response to PEG-RBV in the French Early Access Program for the use of protease inhibitors. Patients received either 12 weeks of telaprevir plus PEG-RBV and a further 36 weeks of PEG-RBV (n=169), or 4 weeks of PEG-RBV followed by 44 weeks of boceprevir plus PEG-RBV (n=138), without randomisation (precludes any comparisons between the two groups). The safety analysis was restricted to patients who received at least 8 weeks of treatment. Serious adverse events occurred in 30% to 51% of patients, which is higher than the rates reported in clinical trials (9-14%).

	Telaprevir (n=169)	Boceprevir (n=138)
Median treatment / PI duration (days)	112.0 / 85.0	113.0 / 84.0
Serious adverse events (SAEs)	87 (51%)	41 (30%)
Discontinuation due to AEs	20 (12%)	10 (7%)
Death	3 (2%)	1 (1%)
Anaemia - Grade 2 (8.0-<10.0g/dL) - Grade 3-4 (<8.0g/dL)	 54 (32%) 23 (14%)	 39 (28%) 8 (6%)
EPO use Blood transfusion	94 (56%) 32 (19%)	71 (51%) 8 (6%)
Neutropenia Grade 3-4 (<1000/mm^3) G-CSF use	21 (12%) 5 (3%)	14 (10%) 7 (5%)
Thrombopenia Grade 3-4 (<50000/mm^3) / Thrombopoietin use	37 (22%) 1 (1%)	10 (7%) 1 (1%)
Rash Grade 3 SCAR	11 (7%) 0 (0%)	1 (1%) 0 (0%)
Grade 3-4 infection Other AEs	4 (2%) 90 (53%)	1 (1%) 44 (32%)

In conclusion, the data strongly suggest that triple therapy must be used with caution and intensive safety monitoring in patients with HCV and compensated cirrhosis.

Comment: The French CUPIC study is evaluating the safety and efficacy of both boceprevir and telaprevir-based triple therapy in patients with established cirrhosis. The interim results were presented for the first time at EASL in April 2012. At the time of presentation, 159 patients had completed at east 12 weeks of treatment with boceprevir. Although on-treatment virologic responses seemed reasonable (70% had undetectable HCV RNA after 12 weeks of boceprevir), tolerability was much poorer than in the Phase III studies (SPRINT-2 and RESPOND-2). The rate of serious adverse events was increased almost 10-fold at 38%. The incidence and severity of anaemia was increased, presumably reflecting increased RBV-haemolysis from renal dysfunction associated with advanced cirrhosis. Of concern was the rate of severe sepsis (9%), hepatic decompensation (4%) and death (2%) despite a short mean treatment duration of only 3.5 months. Similar rates were observed in the patients receiving telaprevir and suggest that these are secondary to adverse effects of interferon in advanced cirrhosis rather than as a direct effect of the protease inhibitors. On post-hoc analysis, those patients with low

Continued on page 6

Continued from page 5

baseline albumin and signs of portal hypertension were at greatest risk for severe complications and death during triple therapy, which suggests that patients with early decompensation (Child Pugh Score 6,7,8) were included in this real-world study. Almost 1/3 patients in this study would have been excluded from the Phase III studies based on the inclusion/exclusion criteria

In both patients receiving boceprevir and those receiving telaprevir, the incidence and severity of anaemia was increased despite very high use of erythropoietin (55-60%). This probably reflects increased RBV exposure because of reduced renal clearance in advanced liver disease.

The results of the CUPIC study suggest that patients with evidence of hepatric decompensation or severe portal hypertension should be treated with caution and preferably in collaboration with the local liver transplant centre.

On a positive note, the early on-treatment virologic responses in cirrhotic patients were similar to those observed in the Phase III registration studies. However, it is early days, and we await the end-of-treatment safety and post-treatment SVR results before we can understand the risk/benefit ratio of treating cirrhotics in the real world with triple therapy. But it is likely that the results from this study will modify the criteria for considering triple therapy in these patients (e.g. Child-Pugh A with no portal hypertension).

Concluding remarks

Less than 2% of individuals with chronic hepatitis C infection have been treated, of whom less than half have been cured. A major barrier to treatment uptake has been the poor efficacy of antiviral regimens especially in HCV genotype 1. The development of the first direct-acting antiviral agents, the first-generation protease inhibitors, has provided hope for many infected with this difficult-to-treat genotype. Results of the Phase III studies of boceprevir-based triple therapy demonstrate significant improvements in efficacy in both treatment-naïve and treatment-experienced patients. In addition, the addition of boceprevir to peginterferon plus ribavirin allowed reduction in treatment duration in most patients. Side-effects, namely anaemia, are predictable and manageable through careful monitoring and ribavirin dose adjustment.

The introduction of boceprevir should increase treatment uptake and also treatment success thereby helping to prevent the projected large health burden associated with chronic hepatitis C.

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