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Dual therapy with the NS5A inhibitor BMS-790052 and the NS3 protease inhibitor BMS-650032 in HCV genotype 1b-infected null responders

Kazuaki Chayama[1], Shoichi Takahashi[1], Joji Toyota[2], Yoshiyasu Karino[2], Kenji Ikeda[3], Hiroki Ishikawa[4], Hideaki Watanabe[4], Fiona McPhee[5], Eric Hughes[6], Hiromitsu Kumada[3]

[1]Hiroshima University, Hiroshima, Japan; [2]Sapporo Kosei General Hospital, Sapporo, Japan; [3]Toranomon Hospital, Tokyo, Japan; [4]Bristol-Myers KK, Tokyo, Japan; [5]Bristol-Myers Squibb Research and Development, Wallingford, CT, USA; [6]Bristol-Myers Squibb Research and Development, Princeton, NJ, USA

Authors' e-mail addresses:

chayama@hiroshima-u.ac.jp; shoichit@hiroshima-u.ac.jp; joji.toyota@ja-hokkaidoukouseiren.or.jp; ykarino@ja-hokkaidoukouseiren.or.jp; ikedakenji@tora.email.ne.jp; hiroki.ishikawa@bms.com; hideaki.watanabe@bms.com; fiona.mcphee@bms.com; eric.hughes@bms.com; kumahiro@toranomon.gr.jp

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Corresponding author:

Kazuaki Chayama, MD, PhD

Department of Medical and Molecular Science, Graduate School of Biomedical Science

Hiroshima University

1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan

E-mail: chayama@hiroshima-u.ac.jp

Phone: +81-82-257-5190

Abbreviations:

HCV, hepatitis C virus

pegIFN, pegylated interferon alfa

RBV, ribavirin

SVR, sustained virologic response: undetectable HCV RNA post-treatment

DAA, direct-acting antiviral

ALT, alanine aminotransferase

ULN, upper limit of the normal reference range

RVR, rapid virologic response: undetectable HCV RNA at week 4

eRVR, extended rapid virologic response: undetectable HCV RNA at weeks 4 and 12

cEVR, complete early virology response: undetectable HCV RNA at week 12

EOTR, end of treatment response: undetectable HCV RNA at week 24

SVR12, sustained virologic response 12 weeks post-treatment

SVR24, sustained virologic response 24 weeks post-treatment

LLOQ, lower limit of quantitation

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Abstract

Patients with chronic hepatitis C virus (HCV) infection and prior null response to peginterferon and ribavirin have limited therapeutic options. HCV genotype 1 is the most common worldwide and the most difficult to treat; genotype 1b is the most common subtype of genotype 1 outside North America. The enhanced antiviral activity achieved by combining two direct-acting antiviral (DAA) agents may improve clinical outcomes. This open-label, phase 2a study included ten patients with chronic HCV genotype 1b infection and prior null response (<2 $\log_{10}$ reduction in HCV RNA after 12 weeks) to peginterferon and ribavirin. Patients received dual DAA treatment for 24 weeks with the NS5A replication complex inhibitor BMS-790052 (60 mg once daily) and the NS3 protease inhibitor BMS-650032 (initially 600 mg twice daily, subsequently reduced to 200 mg twice daily). The primary efficacy endpoint was the proportion of patients with sustained virologic response at 12 weeks post-treatment (SVR_{12}). Nine patients completed 24 weeks of treatment; one patient discontinued treatment after 2 weeks. In the nine patients who completed the full course of treatment, HCV RNA was undetectable at week 8 and remained undetectable through the end of treatment; all nine patients achieved SVR_{12} and SVR_{24}. HCV RNA also remained undetectable post-treatment in the patient who discontinued after 2 weeks. There was no viral breakthrough. Diarrhea and headache, generally mild, were the most common adverse events; transaminase elevations were reported in three patients but did not result in discontinuation. Conclusions: Dual therapy with BMS-790052 and BMS-650032, without peginterferon and ribavirin, can achieve high SVR rates in difficult-to-treat patients with hepatitis C virus genotype 1b infection and prior null response to peginterferon and ribavirin.

Chronic hepatitis C virus (HCV) infection affects approximately 180 million individuals worldwide and is a common cause of chronic liver disease and hepatocellular carcinoma in Japan, the USA, and many European countries.(1, 2) Among the six major HCV genotypes, genotype 1 is the most common and the most difficult to treat, and its two main subtypes may differentially influence therapeutic outcomes.(3, 4) Genotype 1b is the most prevalent worldwide and predominates in Japan and China, while genotype 1a is most common in the USA; subtype prevalence in Europe is similar.(5-7)

Treatment of chronic HCV infection with pegylated interferon alfa (pegIFN) and ribavirin (RBV) elicits a sustained virologic response (SVR) in 40% to 50% of treatment-naïve patients with genotype 1 infections; SVR rates in this population increase to 66% or 75% when boceprevir or telaprevir, respectively, is added to the regimen.(8-12) Response rates are influenced by viral load and genotype and by patient demographics, disease history, and genetics.(10) PegIFN/RBV retreatment of patients with prior non-response to pegIFN/RBV is frequently unsuccessful, with SVR rates of only 6% to 9%.(13, 14) Null responders are the subset of non-responders who have responded most poorly to pegIFN/RBV, and their urgent need for more potent therapies has prompted evaluation of regimens containing direct-acting antivirals (DAAs). SVR rates of 27% (genotype 1a) and 37% (genotype 1b) were achieved in null responders with a regimen combining telaprevir with pegIFN/RBV in a study of non-responders.(15) These results suggest that DAA-containing regimens can benefit this population, but greater antiviral potency is needed to increase response rates further.

Combinations of two DAAs may overcome interferon non-responsiveness in null responders by increasing antiviral activity and reducing the risk of developing resistance-associated variants.(16) In HCV-infected human hepatocyte chimeric mice, dual DAA treatment eradicated HCV without resistance, while resistance emerged rapidly with single DAA treatment.(17) In a clinical study that included null responders, marked antiviral effects were observed after 13 days of dual DAA treatment, supporting the evaluation of longer-term dual DAA therapy reported in this study.(18) BMS-790052 is a first-in-class, highly selective NS5A replication complex inhibitor with picomolar potency and broad genotypic coverage; BMS-650032 is an NS3 protease inhibitor active against HCV genotypes 1a and 1b.(19, 20) BMS-790052 and BMS-650032 are associated with different resistance-associated variants, consistent with their different molecular targets, and showed no meaningful pharmacokinetic interactions in healthy volunteers.(20-22)

In a 24-week study of null responders in the USA, BMS-790052 and BMS-650032 demonstrated potent antiviral effects both as a dual DAA regimen and in a quadruple regimen that included pegIFN/RBV.(23) Overall 36% of dual therapy recipients achieved SVR, including both of the two patients with genotype 1b infection. However, patients with genotype 1a experienced frequent viral breakthrough with the dual regimen and only two of nine achieved SVR, suggesting subtype-associated differences in resistance barrier and response. We present the results of an open-label trial evaluating dual therapy with BMS-790052 and BMS-650032 in Japanese patients with chronic HCV genotype 1b infection and prior null response to pegIFN/RBV.

Methods

Study design

This open label, phase 2a study (clinicaltrials.gov identifier NCT01051414) evaluated the antiviral activity and safety of BMS-790052 combined with BMS-650032 in patients with HCV genotype 1 infection and previous null response to treatment with pegIFN/RBV, defined as <2 $\log_{10}$ reduction of HCV RNA after 12 weeks of therapy. This sentinel cohort provided safety data for review by an independent study safety committee prior to enrolment of additional cohorts that will be described in a subsequent report. Written informed consent was obtained from all patients. The study was approved by institutional review boards at each site and conducted in compliance with the Declaration of Helsinki, Good Clinical Practice Guidelines, and local regulatory requirements.

Patients

Patients eligible for enrolment in the sentinel cohort included men and women aged 20 to 75 years (women of childbearing potential were required to use adequate contraception) with chronic HCV genotype 1 infection for at least 6 months (all enrolled patients were genotype 1b because of the high prevalence of this subtype in Japan) and HCV RNA $\geq 10^5$ IU/mL. Eligible patients met criteria defining null responders and had no evidence of cirrhosis documented by laparoscopy, imaging, or liver biopsy within 2 years.

Patients were excluded if they had a history of hepatocellular carcinoma, co-infection with hepatitis B virus or human immunodeficiency virus, other chronic liver disease, or evidence of hepatic decompensation. Patients were also excluded if they had other severe or unstable

conditions or evidence of organ dysfunction in excess of that consistent with the age of the patient, were unable to tolerate oral medication or had conditions that could impact absorption of study drug, or were exposed to any investigational drug within 4 weeks of study participation or had any previous exposure to inhibitors of NS5A or NS3 protease. Laboratory findings that excluded participation were alanine aminotransferase (ALT) >5 times the upper limit of normal (xULN); total bilirubin ≥2 mg/dL; direct bilirubin >1.5 xULN; INR ≥1.7; albumin ≤3.5 g/dL; hemoglobin <9.0 g/dL; white blood cells <1,500/mm^3; absolute neutrophil count <750/mm^3; platelets <50,000/mm^3; or creatinine >1.8 xULN.

Prohibited concomitant medications included inducers or inhibitors of cytochrome P450/3A4, non-study medications with anti-HCV activity, any prescription medication or herbal product not prescribed for a specific condition, liver protection drugs, proton pump inhibitors, and erythropoiesis-stimulating agents. H2 receptor antagonists were permitted but administered ≥10 hours before or ≥2 hours after BMS-790052; other acid-modifying agents had to be taken ≥2 hours before or after BMS-790052.

Study drug dosing

All patients received oral combination therapy with BMS-790052 and BMS-650032 from the beginning of the study. BMS-790052 was dosed as two 30-mg tablets once daily. BMS-650032 was initially dosed as three 200-mg tablets twice daily; subsequently, the dose of BMS-650032 was reduced to 200 mg twice daily following reports of hepatic enzyme elevations in a clinical study of BMS-650032 and pegIFN/RBV.(24)

Treatment was continued to week 24 for patients with HCV RNA below the assay lower limit of quantitation (LLQ; 15 IU/mL) on or after week 2; treatment was discontinued for patients with <2 $\log_{10}$ IU/mL decrease of HCV RNA from baseline, on or after week 2. For patients with viral rebound on or after week 2, or HCV RNA above LLQ on or after week 4, treatment was discontinued or weight-based pegIFN/RBV therapy was added for up to 48 additional weeks at the investigator's discretion, based on expected tolerance of pegIFN/RBV. Viral rebound was defined as an increase ≥1 $\log_{10}$ IU/mL from nadir at more than one time point, or HCV RNA ≥15 IU/mL after declining to below that level.

Safety and efficacy assessments

Assessments, including HCV RNA, physical examination, vital signs, adverse events, laboratory tests, and review of concomitant medications, were conducted at screening, on study days 1 (baseline) through 7 and days 9, 11, and 14, at weeks 3, 4, 6, 8, 10, 12, 16, 20, and 24, and at post-treatment weeks 4, 8, 12, and 24. Twelve-lead electrocardiograms were recorded at all visits except those at weeks 3 and 6. Additional pre-treatment assessments included HCV genotype and host *IL28B* genotype.

Serum HCV RNA levels were determined at a central laboratory using the Roche COBAS® TaqMan® HCV Auto assay (Roche Diagnostics KK, Tokyo, Japan), lower limit of quantitation=15 IU/mL. HCV genotype and subtype were determined at the central laboratory by PCR amplification and sequencing. *IL28B* genotype was determined by PCR amplification and sequencing of the rs12979860 single-nucleotide polymorphism.

Outcome measures

The primary efficacy endpoint was the proportion of patients with undetectable HCV RNA at 12 weeks post-treatment (SVR_{12}). Secondary endpoints included the proportions of patients with rapid virologic response (RVR, defined as undetectable HCV RNA at week 4), extended RVR (eRVR, undetectable HCV RNA at weeks 4 and 12), complete early virologic response (cEVR, undetectable HCV RNA at week 12), end of treatment response (EOTR, undetectable HCV RNA at week 24), and SVR at 24 weeks post-treatment (SVR_{24}).

The possible presence of HCV resistance polymorphisms was analyzed using stored specimens. Resistance testing was performed on all samples at baseline and on samples indicative of virologic failure, defined as either a) <2 $\log_{10}$ HCV RNA decrease from baseline at week 2, b) virologic rebound (HCV RNA detectable after previously undetectable or ≥1 $\log_{10}$ increase from nadir), or c) detectable HCV RNA at weeks 4 or 12 or at the end of therapy. Resistance analysis methodology included isolation of HCV RNA, PCR amplification, and population sequencing of HCV NS3 protease and NS5A domains.

Statistical analysis

Categorical variables were summarized using counts and percents; continuous variables were summarized with univariate statistics.

Results

Patient characteristics and disposition

Twelve patients were screened; two failed to meet entry criteria (for hepatocellular carcinoma and elevated direct bilirubin, respectively) and 10 patients were enrolled and treated. Enrolled patients were generally older (median 62 years); six were female and all were Japanese (table 1). All enrolled patients were infected with genotype 1b, reflecting the predominance of this subtype in Japan, although the study protocol did not exclude patients with HCV genotype 1a.(6) Two patients were *IL28B* genotype CC (single-nucleotide polymorphism rs12979860) and eight were CT. Nine patients completed 24 weeks of therapy; one patient discontinued at week 2 due to a grade 4 total bilirubin elevation (see **Safety**). Among the nine patients treated for 24 weeks, BMS-650032 was dosed at 600 mg twice daily for 12 to 21 weeks before the dose was reduced to 200 mg twice daily (figure 1).

Virologic response

Serum HCV RNA levels decreased rapidly in all patients (figure 2); mean reductions from baseline were 4.4 $\log_{10}$ IU/mL at week 1, 5.3 $\log_{10}$ IU/mL at week 2, and 5.8 $\log_{10}$ IU/mL from week 4 through the end of treatment. At week 4, HCV RNA was undetectable (RVR) in four of ten (40%) patients and below the assay LLQ in nine of ten (90%; figure 3). No patients qualified for discontinuation or addition of pegIFN/RBV. At week 8, HCV RNA was undetectable in nine of ten patients (all who remained on treatment) and remained undetectable through the end of treatment and follow-up. SVR_{12}, the primary endpoint, and SVR_{24} were achieved by 90% of patients including all nine who completed 24 weeks of therapy. The patient who discontinued

treatment at week 2 had low-level HCV RNA at discontinuation (1.8 $\log_{10}$ IU/mL), but HCV RNA was undetectable at follow-up visits 2, 3, 4, 13, and 24 weeks after discontinuation.

Viral breakthrough and relapse

There was no viral breakthrough during treatment or relapse of HCV RNA post-treatment. Analysis of baseline samples revealed variants reported to confer minimal to low levels of resistance to BMS-790052.(22) NS5A substitutions L28M and L31M were detected in one patient each and Y93H was detected in two other patients. NS3 protease substitutions reported to confer resistance to telaprevir, boceprevir, and TMC-435 were detected;(25) T54S was identified in one patient and Q80L was identified in three. In one patient, both NS3 protease substitutions (T54S, Q80L) and an NS5A substitution (Y93H) were detected. There was no consistent association between detection of these variants and virologic outcomes.

Safety

The most frequently reported adverse events were diarrhea and headache, all mild (grade 1) (table 2). The patient who discontinued (see below) experienced multiple grade 3 or 4 adverse events and laboratory abnormalities on treatment. In the other nine patients, there were no grade 3 or 4 transaminase elevations or other grade 3 or 4 events, no clinically relevant changes in electrocardiogram parameters, and no lymphopenia of any severity. Two transient grade 1 ALT elevations were reported, and one grade 2 elevation that began at week 16 and persisted until the end of treatment, after which it normalized within two weeks (figure 1). There were no notable differences in ALT before and after BMS-650032 dose reduction.

There were two serious adverse events. A 54 year-old male was hospitalized with grade 3 pyrexia and persistent diarrhea 11 days after initiating study treatment. Loxoprofen was initiated, and body temperature normalized and diarrhea improved after four days. The patient remained on study treatment. The second event concerned a 60 year-old woman with a history of ulcerative colitis who discontinued study treatment after two weeks due to a grade 4 bilirubin elevation with multiple complicating features. Five days before discontinuation, she presented with infectious gastroenteritis and was treated with cefotiam and subsequently hospitalized with fever, vomiting, and diarrhea. Meropenem, human serum albumin, and furosemide were initiated. At discontinuation of study drugs, laboratory findings included total bilirubin of 7.7 mg/dL and grade 3 lymphopenia and serum phosphorus reduction; transaminases and alkaline phosphatase were within normal ranges. In the week following discontinuation, white cell and eosinophil counts became elevated; total bilirubin improved and transaminases remained normal. Two weeks after discontinuation, grade 4 ALT and aspartate aminotransferase (AST) elevations and a grade 3 lipase elevation were reported. Six weeks after discontinuation, bilirubin and transaminase elevations were resolved and lipase improved to within 2 xULN.

Discussion

This study assessed combination oral DAA therapy in a difficult-to-treat population with multiple adverse prognostic features, including HCV genotype 1b infection, primarily *IL28B* CT genotype, generally older age, and null response to previous pegIFN/RBV therapy.(10, 13, 14) These patients represent a group with a significant need for new therapeutic options.

A DAA-only therapeutic strategy may be particularly appropriate for null responders, who have previously shown only marginal response to pegIFN/RBV.(13, 14) The combination of two highly potent DAAs cleared detectable virus rapidly in this study; HCV RNA was undetectable by week 8 in all nine patients treated for 24 weeks. This outcome compares favorably with those observed when null responders received a combination of pegIFN/RBV and a single NS3 protease inhibitor, telaprevir or TMC435.(15, 26) In these studies HCV RNA remained detectable in 36% to approximately 50% of patients after 12 weeks.

HCV RNA remained undetectable 12 weeks (SVR_{12}) and 24 weeks (SVR_{24}) post-treatment in all patients who completed treatment. This contrasts with the poor results obtained with pegIFN/RBV retreatment and the reported 37% SVR rate of genotype 1b null responders who received pegIFN/RBV and telaprevir.(10, 13-15) Additional follow-up of patients from this study will assess whether SVR_{24} is predictive of long-lasting viral clearance with this dual DAA therapy, as it is with pegIFN/RBV. It is interesting that HCV RNA was persistently undetectable post-treatment in the patient who discontinued after only two weeks of treatment. With early discontinuation data from only this single case, at present the result must be considered an anomaly. The factors that contributed to viral clearance are uncertain, although the patient's *IL28B* CC genotype suggests increased sensitivity to endogenous interferon;(27) the possible influence of concurrent acute gastroenteritis or other complicating factors is unknown. However, coupled with the attainment of SVR_{12} in all other patients, this outcome suggests that required duration of therapy, which is currently predicated on data from pegIFN-based regimens, may need reassessment for DAA-only regimens, and possibly that certain patient populations can be treated for very short durations.

The high SVR rate is consistent with limited data from a related USA-based study, in which 2 of 2 null responders with HCV genotype 1b and treated with BMS-790052 and BMS-650032 achieved SVR_{24}.(23) However, only 2 of 9 patients with genotype 1a achieved SVR_{24} with the dual DAA regimen, compared with 9 of 10 patients who received both DAAs and pegIFN/RBV. These differences suggest that viral genotype can influence responses to DAA regimens that do not include pegIFN/RBV, and outcomes can be optimized with individualized therapy that considers viral genotype, among other factors. Because of the high SVR rate, the potential influence of other baseline and on-treatment parameters cannot be assessed, other than to observe that unfavorable predictors of pegIFN/RBV response, such as older age and *IL28B* CT genotype,(27, 28) had no measureable impact on outcomes.

There was no viral breakthrough on treatment. In view of the rapid emergence of resistance in some studies of short-term DAA monotherapy,(29, 30) these findings support the concept that dual DAA therapy reduces the risk of viral breakthrough in addition to increasing antiviral activity. Resistance analyses revealed that before treatment, some patients carried NS5A and NS3 polymorphisms predicted to reduce sensitivity to BMS-790052 and some HCV protease inhibitors, respectively.(22, 25) There was no clear relationship between the presence of these polymorphisms and minor inter-patient differences in the rate of early virologic response; however, further study in larger patient cohorts will help determine whether baseline polymorphisms can influence virologic response with this regimen.

The adverse event profile of the dual DAA regimen compares favorably with the more frequent and severe events reported with pegIFN/RBV, although patient numbers in this study were limited. The mild diarrhea experienced by several patients has been reported previously with BMS-650032 and is common with other drugs of this class.(15, 18, 24) While a role for BMS-790052 and/or BMS-650032 in the two serious adverse events cannot be ruled out and the investigator considered these events drug-related, multiple confounding factors existed. The case of pyrexia was consistent with a viral infection and resolved with treatment. In the case of hyperbilirubinemia that led to discontinuation, the time course of laboratory abnormalities and related events suggests a link to the use of cefotiam and meropenem for treatment of infectious gastroenteritis. Both of these agents have been associated with vomiting, diarrhea, and hyperbilirubinemia.(31, 32)

The BMS-650032 dose was reduced during treatment due to transaminase elevations observed with 600 mg twice daily in a concurrent study.(24) In this sentinel cohort, viral suppression was maintained in all patients after dose reduction, and no grade 3 or 4 transaminase elevations occurred during treatment at either dose of BMS-650032. One patient experienced grade 2 transaminase elevations that began at week 16 and persisted during treatment despite BMS-650032 dose reduction at week 19. Although these elevations were not severe, their rapid normalization post-treatment suggests a possible relationship to study treatment. None of the nine patients treated for 24 weeks experienced transaminase elevations post-treatment. Although grade 4 transaminase elevations occurred two weeks post-treatment in the patient who discontinued, the timing of these events and multiple other complications suggest that they were not related directly to study treatment.

In conclusion, the combination of BMS-790052 and BMS-650032 achieved a high rate of SVR_{24} in patients with HCV genotype 1b infections and prior null response to pegIFN/RBV. These results support the concept that HCV infection can be cured with two DAAs without pegIFN/RBV even in difficult-to-treat populations that lack robust interferon responsiveness. Further research will assess the benefits of DAA combinations in larger and more diverse patient populations.

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