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RAPID COMMUNICATION

Daclatasvir Plus Asunaprevir for Chronic HCV Genotype 1b Infection

Hiromitsu Kumada,[1] Yoshiyuki Suzuki,[1] Kenji Ikeda,[1] Joji Toyota,[2] Yoshiyasu Karino,[2] Kazuaki Chayama,[3] Yoshiiku Kawakami,[3] Akio Ido,[4] Kazuhide Yamamoto,[5] Koichi Takaguchi,[6] Namiki Izumi,[7] Kazuhiko Koike,[8] Tetsuo Takehara,[9] Norifumi Kawada,[10] Michio Sata,[11] Hidetaka Miyagoshi,[12] Timothy Eley,[13] Fiona McPhee,[13] Andrew Damokosh,[13] Hiroki Ishikawa,[12] and Eric Hughes[13]

All-oral combinations of direct-acting antivirals may improve efficacy and safety outcomes for patients with hepatitis C virus (HCV) infection, particularly those who are poor candidates for current interferon/ribavirin-based regimens. In this open-label, phase 3 study, 135 interferon-ineligible/intolerant and 87 nonresponder patients with chronic HCV genotype 1b infection were enrolled at 24 centers in Japan. Patients received daclatasvir 60 mg once daily plus asunaprevir 100 mg twice daily for 24 weeks. The primary endpoint was sustained virologic response 24 weeks after treatment (SVR_{24}). This study is registered with Clinical Trials.gov (NCT01497834). SVR_{24} was achieved by 87.4% of interferon-ineligible/intolerant patients and 80.5% of nonresponder (null and partial) patients; rates were similar in cirrhosis (90.9%) and noncirrhosis (84.0%) patients, and in patients with *IL28B* CC (84.5%) or non-CC (84.8%) genotypes. Fourteen patients in each group (12.6%) discontinued dual therapy, mainly due to adverse events or lack of efficacy. Nine nonresponder patients received additional treatment with peginterferon/ribavirin per protocol-defined criteria. The rate of serious adverse events was low (5.9%) and varied among patients. The most common adverse events were nasopharyngitis, increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST), headache, diarrhea, and pyrexia. *Conclusion:* Interferon-free, ribavirin-free all-oral therapy with daclatasvir and asunaprevir for 24 weeks is well tolerated and can achieve a high rate of SVR in patients with HCV genotype 1b who were ineligible, intolerant, or had not responded to prior interferon-based therapy. (HEPATOLOGY 2014;59:2083-2091)

Treatment of chronic hepatitis C virus (HCV) infection typically includes a regimen of interferon-based therapy plus ribavirin, with or without a direct-acting antiviral. The efficacy and tolerability of these regimens are not ideal, and there remains a large number of patients for whom these treatments are not acceptable or viable. The addition of direct-acting antivirals can improve treatment outcomes for patients infected with chronic HCV. When combined with peginterferon and ribavirin, the HCV protease inhibitors telaprevir, boceprevir, or simeprevir achieved overall sustained virologic response (SVR) rates ranging from 68% to 89% in treatment-naïve patients with HCV genotype 1 infection.[1-3] Patients with no response to previous peginterferon/ribavirin therapy did not respond as well to this combined regimen, with rates of SVR ranging from 34% to 52%.[3-5] In Japan, patients chronically infected with HCV are older and predominantly infected with HCV genotype 1, both factors which impact response to therapy.[6] For Japanese patients who had no prior response to treatment with peginterferon/ribavirin, telaprevir or

Abbreviations: HCV, hepatitis C virus; LLOQ, lower limit of quantitation; NS, nonstructural; SVR, sustained virologic response; TD, target detected; TND, target not detected.

From the [1]Toranomon Hospital, Tokyo, Japan; [2]Sapporo-Kosei General Hospital, Sapporo, Japan; [3]Hiroshima University, Hiroshima, Japan; [4]Kagoshima University, Kagoshima, Japan; [5]Okayama University, Okayama, Japan; [6]Kagawa Prefectural Central Hospital, Kagawa, Japan; [7]Musashino Red Cross Hospital, Tokyo, Japan; [8]University of Tokyo, Tokyo, Japan; [9]Osaka University, Osaka, Japan; [10]Osaka City University, Osaka, Japan; [11]Kurume University, Fukuoka, Japan; [12]Bristol-Myers KK, Tokyo, Japan; [13]Bristol-Myers Squibb Research & Development, Princeton, NJ, USA.

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simeprevir plus peginterferon and ribavirin provided SVR rates of only 34% or 38-51%, respectively.[3,7] The array of adverse events associated with peginterferon and ribavirin is well known; incremental toxicities associated with the addition of telaprevir to peginterferon and ribavirin included anemia, skin disorders and severe rash, and gastrointestinal-related disorders, while the addition of simeprevir is associated with hyperbilirubinemia due to inhibition of hepatic bilirubin transporters.[3] For patients who cannot tolerate or are not eligible for treatment with interferon-based therapy because of coexisting morbidities, treatment options are few to none. Clearly, the current treatment options are not adequate and an urgent unmet need remains for better treatment regimens for these patient populations.

Daclatasvir is a first-in-class, NS5A replication complex inhibitor with potent pan-genotypic antiviral activity *in vitro* (HCV genotypes 1-6).[8] Asunaprevir is a potent, selective NS3 protease inhibitor with antiviral activity against HCV genotypes 1, 4, 5, and 6 *in vitro*.[9] Both daclatasvir and asunaprevir have demonstrated robust antiviral activity, with no clinically meaningful pharmacokinetic interactions between them when coadministered.[8,10,11] Preliminary phase 2 studies showed potent antiviral effects using daclatasvir and asunaprevir as an all-oral therapy and in combination with a regimen of peginterferon/ribavirin in patients infected with HCV genotype 1 who had not responded to prior therapy.[12,13] We evaluated the safety and antiviral activity of interferon-free, ribavirin-free, all-oral therapy with daclatasvir and asunaprevir in a phase 3 trial involving Japanese patients infected with HCV genotype 1b who are interferon-ineligible/intolerant or nonresponders (null and partial) to interferon-based therapies.

Materials and Methods

Patients. A total of 259 patients were enrolled at 24 centers in Japan from January 5 2012 to March 30 2012. Eligible patients were men and women, 20 to 75 years of age, with chronic HCV genotype 1b infection, an HCV RNA level of 10^5 IU/mL or higher, with a body-mass index of 16 to 35 kg/m^2, and, in up to 10% of enrolled patients, evidence of compensated cirrhosis (Child-Pugh A), as documented either by liver biopsy or discriminated by a previously described algorithm.[14]

Key exclusion criteria included evidence of hepatocellular carcinoma, coinfection with hepatitis B virus or human immunodeficiency virus, or previous exposure to inhibitors of NS5A or NS3 protease. Patients with alanine aminotransferase (ALT) of more than 5 times the upper limit of normal range, total bilirubin of 2 mg/dL or higher, an international normalized ratio of 1.7 or higher, an albumin level 3.5 g/dL or below, and a platelet count of less than 50,000/mm^3 were also excluded.

Patients ineligible for interferon-based therapy, but potentially eligible for enrolment in this study, were treatment-naïve and considered poor candidates for interferon-based therapy because of medical complications including anemia, neutropenia, thrombocytopenia, depression, advanced age (≥65 years), or other conditions deemed not suitable for interferon-based therapy by the investigator, including hypertension, diabetes mellitus, autoimmune disease, and abnormal thyroid function. Patients intolerant to interferon-based therapy had received interferon-based therapy for less than 12 weeks and previously discontinued from therapy due to toxicities associated with interferon or ribavirin. Patients who were null or partial responders to previous peginterferon/ribavirin or interferon-beta/ribavirin therapy were defined as never having attained an undetectable HCV RNA level after at least 12 weeks of therapy. Null responders included patients who never attained at least a 2-$\log_{10}$ decrease from baseline in HCV RNA levels at week 12, and partial responders never achieved undetectable HCV RNA levels after 12 weeks of therapy.

Study Design. In this open-label, phase 3 study of two patient cohorts, interferon-ineligible/intolerant and

Address reprint requests to: Eric Hughes, M.D., Bristol-Myers Squibb, Rte. 206 & Province Line Road, Princeton, NJ, 08543. E-mail: eric.hughes@bms.com; fax: 609-252-7900.

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nonresponder patients received daclatasvir and asunaprevir for 24 weeks. Patients were followed for an additional 24 weeks after treatment. Daclatasvir was administered orally at a dose of 60 mg once daily, and asunaprevir was administered orally at a dose of 100 mg twice daily. Host *IL28B* genotype was assayed for the rs12979860 single-nucleotide polymorphism by Monogram Biosciences using a real-time polymerase chain reaction (PCR) assay.

Nonresponder patients who met futility criteria, defined as an increase in viral load of at least 1 $\log_{10}$ or confirmed detectable HCV RNA of at least 15 IU/mL on or after week 8, were eligible for addition of peginterferon-alpha/ribavirin to continued treatment with daclatasvir and asunaprevir for an additional 24 weeks at the discretion of the investigator. Interferon-ineligible/intolerant patients were not candidates for interferon-based therapy; therefore, daclatasvir/asunaprevir dual therapy was stopped if futility criteria were met.

Study Oversight. This study was approved by the Institutional Review Board at each participating site and was conducted in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. All patients provided written informed consent.

Efficacy Assessments. HCV RNA levels were measured using the Roche COBAS Taqman test with a lower and an upper limit of quantitation of 15 IU/mL and 6.9 $\times$ 10^7 IU/mL, respectively. HCV RNA was measured at screening and at day 1, weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, and 24, and posttreatment at weeks 4, 8, 12, and 24.

Resistance Testing. Patient-derived HCV NS5A and NS3/4A sequence populations were PCR-amplified and sequenced. Patient samples selected for sequencing included all baseline samples and samples from patients with virologic failure.

Safety Assessments. Safety evaluations included reported adverse events and serious adverse events, clinical laboratory tests, physical examinations, and electrocardiograms.

Endpoints. The primary efficacy endpoint was the proportion of patients with HCV RNA <15 IU/mL (target detected [TD] or target not detected [TND]) at 24 weeks after completion of daclatasvir and asunaprevir treatment, including patients who discontinued treatment early. Key secondary endpoints included the proportion of patients with undetectable HCV RNA (TND) at weeks 4 and 12, at the end of treatment, and HCV RNA <15 IU/mL (TD or TND) at 12 weeks after the end of treatment. Safety endpoints included the frequency of serious adverse events, adverse events, discontinuations due to adverse events, and laboratory abnormalities.

Statistical Analysis. Analyses included all patients who received at least one dose of study medications. For virologic response, 2-sided 95% confidence intervals were calculated based on the normal approximation to the binomial distribution. Categorical variables were summarized using counts and percents. Continuous variables were summarized with univariate statistics. Patients with missing data or those who received additional peginterferon/ribavirin therapy were considered failures.

Role of the Funding Source. The study was designed and conducted by the sponsor (Bristol-Myers Squibb/Bristol-Myers KK) in collaboration with the principal investigators. The sponsor collected the data, monitored the study conduct, and performed the statistical analyses. All authors had access to the data and assume responsibility for the accuracy, integrity, and completeness of the reported data and for the fidelity of this report to the trial protocol. The article was prepared by authors employed by Bristol-Myers Squibb, with input from all authors and the assistance of a medical writer employed by Bristol-Myers Squibb. All authors made the decision to submit the article for publication.

Results

Patients. In all, 222 patients received treatment, 135 in the interferon-ineligible/intolerant group (100 medically ineligible for interferon, 35 intolerant to interferon) and 87 in the nonresponder group (48 null responders, 36 partial responders, 3 undetermined) (Fig. 1). Demographic baseline characteristics of patients are shown in Table 1. As expected, when compared with reported demographics from U.S. and European studies, patients were older and a larger proportion were female. Similar to the global population, however, there were more patients with *IL28B* CC genotype in the interferon-ineligible/intolerant population (69.6%) and more patients with *IL28B* non-CC genotype in the nonresponder population (81.6%). Overall, the rate of discontinuations from dual therapy was low (12.6%; 14 patients in each group), and was due primarily to adverse events (nine patients [6.7%] in the interferon-ineligible/intolerant group, two patients [2.3%] in the nonresponder group) and lack of efficacy (four patients [3.0%] in the interferon-ineligible/intolerant group, 11 patients [12.6%] in the nonresponder group).

Virologic Response. HCV RNA levels declined rapidly after initiation of treatment in both groups (Fig. 2). At week 2, the mean decrease in HCV RNA

Table 1. Demographic and Baseline Characteristics of Patients and Their Disease

Characteristic	Interferon-Ineligible/Intolerant n = 135	Nonresponder n = 87	Total N = 222
Age, years			
- Median	64.0	60.0	62.5
- Range	24-75	42-74	24-75
- ≥65 years, n (%)	62 (45.9)	27 (31.0)	89 (40.1)
Male sex, n (%)	38 (28.1)	39 (44.8)	77 (34.7)
IL28B rs12979860 genotype, n (%)			
- CC	94 (69.6)	16 (18.4)	110 (49.5)
- CT	40 (29.6)	66 (75.9)	106 (47.7)
- TT	1 (0.7)	5 (5.7)	6 (2.7)
HCV RNA			
- Mean $\log_{10}$ IU/mL ± SD	6.6 ± 0.58	6.8 ± 0.47	6.6 ± 0.55
- ≥800,000 IU/mL, n (%)	109 (80.7)	80 (92.0)	189 (85.1)
Cirrhosis, n (%)	11 (8.1)	11 (12.6)	22 (9.9)
Response to prior therapy (nonresponders), n (%)			
- Null	NA	48 (55.2)	48 (21.6)
- Partial	NA	36 (41.4)	36 (16.2)
- Other	NA	3 (3.4)*	3 (1.4)
Premedical status (interferon-ineligible/intolerant), n (%)			
- Ineligible-naïve	100 (74.1)	NA	100 (45.0)
• Depression	10 (10.0)	NA	10 (10.0)
• Anemia/neutropenia/thrombocytopenia	44 (44.0)	NA	44 (44.0)
• Other complications requiring medications†	34 (34.0)	NA	34 (34.0)
• Advanced age	12 (12.0)	NA	12 (12.0)
- Intolerant	35 (25.9)	NA	35 (15.8)

*Three patients had insufficient data to be classified as partial or null nonresponders.
†Other complications included hypertension, diabetes mellitus, autoimmune disease, abnormal thyroid function, insomnia, stroke, and psychological.
NA = not applicable.

from baseline was 5.2 $\log_{10}$ IU/mL. Overall, 167/222 patients (75.2%) had undetectable HCV RNA at week 4 during treatment, and 202 patients (91.0%) had undetectable HCV RNA at week 12 on treatment. At 12 weeks after the end of treatment period, 119 (88.1%) interferon-ineligible/intolerant and 70 (80.5%) nonresponder patients had achieved SVR_{12}; by 24 weeks after the end of treatment 118 (87.4%) interferon-ineligible/intolerant and 70 (80.5%) nonresponder patients had achieved SVR_{24} (Table 2). Patients with cirrhosis also achieved high rates of SVR_{24} (20/22, 90.9%). When analyzed by *IL28B* genotype, the response rates were similar for patients with *IL28B* CC genotype (84.5%) and *IL28B* non-CC genotypes (84.8%) (Table 2). Other baseline factors including gender, age, and baseline HCV RNA, did not appear to impact response rates (Table 2).

Virologic Failure. Thirty-four (15.3%) patients (17 each in the interferon-ineligible/intolerant group and nonresponder group) were considered virologic failures. Of patients with undetectable HCV RNA at the end of treatment, 11/129 (8.5%) interferon-ineligible/intolerant patients experienced viral relapse during posttreatment follow-up. Six of 76 patients (7.9%) in the nonresponder group with undetectable HCV RNA at the end of treatment had viral relapse. Two patients in the interferon-ineligible/intolerant group and one patient in the nonresponder group had detectable HCV RNA at the end of treatment. Virologic breakthrough occurred in 4 (3.0%) interferon-ineligible/intolerant patients and in 10 (11.5%) nonresponder patients. At the discretion of the investigators, 9 of the 10 nonresponder patients with virologic breakthrough had additional treatment with peginterferon/ribavirin according to protocol-defined criteria; all nine patients were declared treatment failures in the analysis of the primary endpoint. One of the nine patients who received additional peginterferon/ribavirin responded to treatment with no detectable HCV RNA at follow-up week 24, two patients had HCV RNA detectable at end of treatment, and six patients relapsed.

Of the 34 patients with virologic failure, 29 had resistance-associated substitutions to both daclatasvir (predominantly NS5A-L31M/V-Y93H) and asunaprevir (predominantly NS3-D168 variants) detected at failure. Twenty-two patients with virologic failure had NS5A polymorphisms L31M/V and/or Y93H prior to treatment (Supporting Table 1).

We also investigated the influence of pretreatment resistance-associated variants on efficacy in this study. Pretreatment L31M, Y93H, or linked L31V+Y93H NS5A polymorphisms were detected in 7, 29, and 1 of the 214 patients with available baseline NS5A

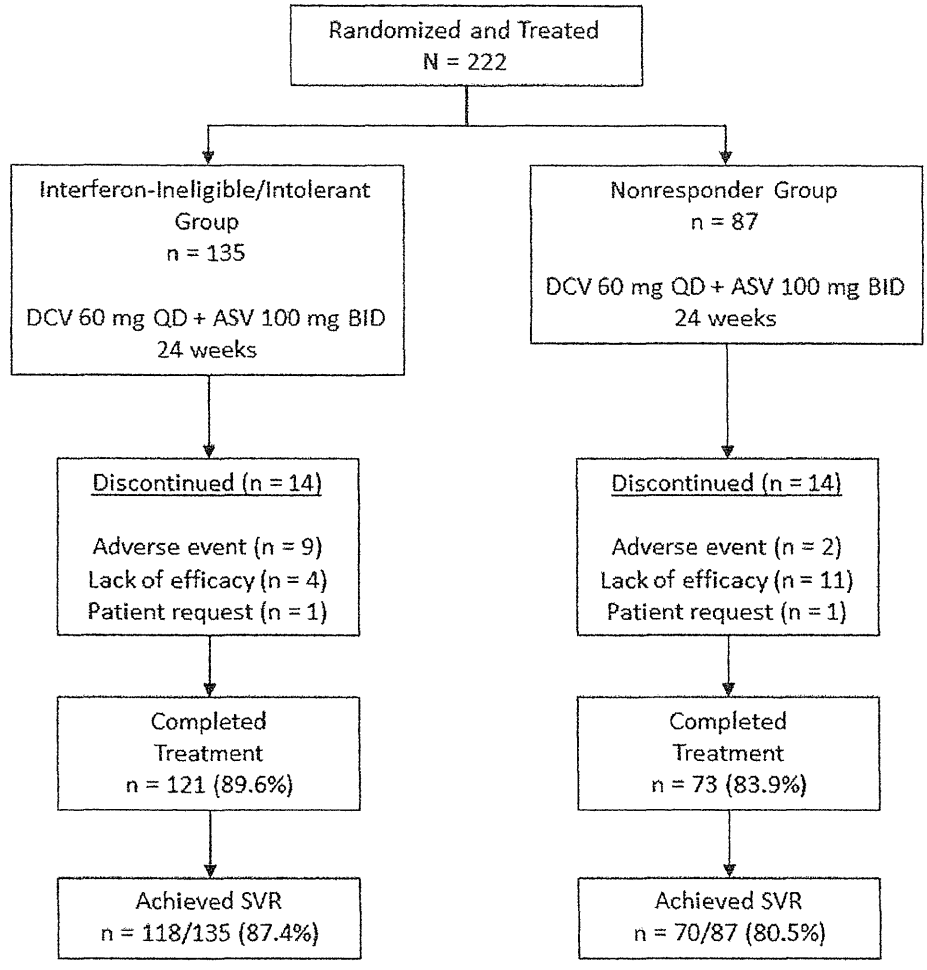

Fig. 1. Patient disposition.

sequences, respectively. Of the 37 patients with L31M/V and/or Y93H at baseline, 11/23 interferon-ineligible/intolerant patients and 4/14 nonresponder patients achieved SVR. The primary asunaprevir resistance-associated variant, NS3-D168E, was present in 2/221 patients with available baseline NS3 sequences; neither of these patients had concomitant NS5A resistance-associated variants. One of these patients achieved SVR; the other relapsed posttreatment.

In comparison with patients who achieved SVR, patients with virologic failure were more likely to have daclatasvir and asunaprevir trough concentrations below their respective median values but within the expected range (Supporting Fig. 1). Most patients with trough concentrations below median values achieved SVR. Treatment compliance, assessed by pill counts and interviews at each study visit, was 83.9% in prior nonresponders and 88.9% in interferon-ineligible/intolerant patients. Across both cohorts, patients with ≥95% compliance in dose and duration of treatment had an SVR_{24} rate of 92.7% (179/193), compared with a 31.0% (9/29) SVR_{24} rate in patients who were <95% compliant (15 out of the 29 patients were discontinued due to the lack of efficacy).

Safety. A total of 194 patients (87.4%) completed 24 weeks of therapy, 121 (89.6%) in the interferon-ineligible/intolerant group and 73 (83.9%) in the nonresponder group. No deaths occurred during the study period. Eleven patients (5.0%) discontinued after 4 to 23 weeks of treatment; 10 discontinued due to ALT and aspartate aminotransferase (AST) elevations and one patient discontinued due to myasthenia gravis, with subsequent detection of preexisting myasthenia gravis-related antibodies.

The most common adverse events were nasopharyngitis, increased ALT and AST, headache, diarrhea, and pyrexia (Table 3). Serious adverse events were reported in 13 (5.9%) patients during treatment. In nine (6.7%) interferon-ineligible/intolerant patients, these events included periarthritis, schizoaffective disorder, myasthenia gravis, myocardial infarction, pyrexia, appendicitis, pyelonephritis,

Table 2. Virologic Outcomes

Virologic Response, n (%) [95% CI]	Interferon-Ineligible/Intolerant n = 135	Nonresponder n = 87	Total N = 222
Week 4,*	114 (84.4)	53 (60.9)	167 (75.2)
	[78.3, 90.6]	[50.7, 71.2]	[69.5, 80.9]
Week 12,*	125 (92.6)	77 (88.5)	202 (91.0)
	[88.2, 97.0]	[81.8, 95.2]	[87.2, 94.8]
Weeks 4 and 12,*	106 (78.5)	48 (55.2)	154 (69.4)
	[71.6, 85.4]	[44.7, 65.6]	[63.3, 75.4]
End of treatment response*	129 (95.6)	76 (87.4)	205 (92.3)
	[92.1, 99.0]	[80.4, 94.3]	[88.8, 95.8]
Sustained virologic response	126 (93.3)	71 (81.6)	197 (88.7)
4 weeks after treatment (SVR_4)†	[89.1, 97.5]	[73.5, 89.7]	[84.6, 92.9]
Sustained virologic response	119 (88.1)	70 (80.5)	189 (85.1)
12 weeks after treatment (SVR_{12})†	[82.7, 93.6]	[72.1, 88.8]	[80.5, 89.8]
Sustained virologic response	118 (87.4)	70 (80.5)	188 (84.7)
24 weeks after treatment (SVR_{24})†	[81.8, 93.0]	[72.1, 88.8]	[79.9, 89.4]
SVR_{24} by subpopulations			
- Null responders	N/A	39/48 (81.3)	39/48 (81.3)
- Partial responders	N/A	28/36 (77.8)	28/36 (77.8)
- Undetermined	N/A	3/3 (100)	3/3 (100)
- Ineligible-naïve	85/100 (85.0)	N/A	85/100 (85.0)
- Intolerant	33/35 (94.3)	N/A	33/35 (94.3)
- Cirrhosis	10/11 (90.9)	10/11 (90.9)	20/22 (90.9)
- Noncirrhosis	108/124 (87.1)	60/76 (78.9)	168/200 (84.0)
- Male	32/38 (84.2)	32/39 (82.1)	64/77 (83.1)
- Female	86/97 (88.7)	38/48 (79.2)	124/145 (85.5)
- Age $<$ 65 years	61/73 (83.6)	47/60 (78.3)	108/133 (81.2)
- Age $\geq$ 65 years	57/62 (91.9)	23/27 (85.2)	80/89 (89.9)
- HCV RNA $<$ 800,000 IU/mL	25/26 (96.2)	6/7 (85.7)	31/33 (93.9)
- HCV RNA $\geq$ 800,000 IU/mL	93/109 (85.3)	64/80 (80.0)	157/189 (83.1)
SVR_{24} by *IL28B* genotype (rs12979860)			
- CC	79/94 (84.0)	14/16 (87.5)	93/110 (84.5)
- CT	38/40 (95.0)	52/66 (78.8)	90/106 (84.9)
- TT	1/1 (100)	4/5 (80)	5/6 (83.3)
Virologic failures			
- Virologic breakthrough	4 (3.0)	10 (11.5)‡	14 (6.3)
- End of treatment detectable	2 (1.5)	1 (1.1)	3 (1.4)
- Relapse (among patients undetectable at end of treatment)	11/129 (8.5)	6/76 (7.9)	17/205 (8.3)

*HCV RNA <LLOQ (<15 IU/mL), target not detected.
†HCV RNA <LLOQ, target detected or target not detected.
‡9/10 patients received additional treatment with peginterferon/ribavirin according to protocol criteria.

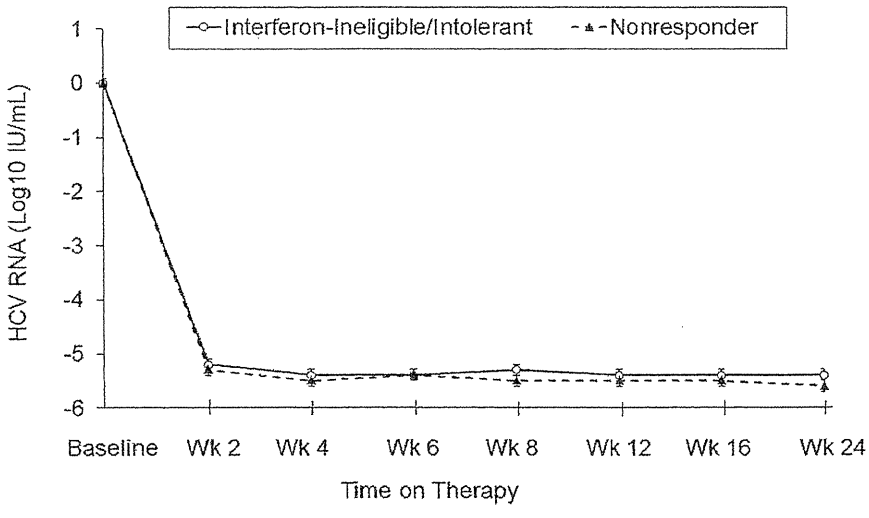

Fig. 2. Mean change in HCV RNA during treatment with daclatasvir and asunaprevir in interferon-ineligible/intolerant and nonresponder patients.

Table 3. Adverse Events and Grade 3-4 Laboratory Abnormalities During the Treatment Period

Event or Laboratory Abnormality, n (%)	Interferon-Ineligible/Intolerant n = 135	Nonresponder n = 87	Total N = 222
Serious adverse events (on treatment)	9 (6.7)	4 (4.6)	13 (5.9)
Adverse event*			
Nasopharyngitis	40 (29.6)	27 (31.0)	67 (30.2)
Increased ALT	24 (17.8)	11 (12.6)	35 (15.8)
Increased AST	18 (13.3)	10 (11.5)	28 (12.6)
Headache	18 (13.3)	17 (19.5)	35 (15.8)
Diarrhea	12 (8.9)	10 (11.5)	22 (9.9)
Pyrexia	12 (8.9)	15 (17.2)	27 (12.2)
Grade 3-4 laboratory abnormality			
Alanine aminotransferase	12 (8.9)	4 (4.6)	16 (7.2)
Aspartate aminotransferase	10 (7.4)	2 (2.3)	12 (5.4)
Hemoglobin	6 (4.4)	1 (1.1)	7 (3.2)
Lymphocytes	5 (3.7)	1 (1.1)	6 (2.7)
Platelets	2 (1.5)	2 (2.3)	4 (1.8)
Bilirubin, total	1 (0.7)	1 (1.1)	2 (0.9)
Neutrophils	0	1 (1.1)	1 (0.5)
Creatinine	1 (0.7)	0	1 (0.5)
Lipase, total	1 (0.7)	0	1 (0.5)

*Adverse events that occurred in more than 10% of patients in any group.

basal cell carcinoma, and hepatocellular carcinoma, respectively; events in four (4.6%) nonresponder patients included second-degree burn, increased liver enzymes, esophageal variceal hemorrhage, and herpes zoster.

ALT and AST elevations were the most frequent adverse events and grade 3/4 laboratory abnormalities (Table 3) and were the basis for 10 of the 11 discontinuations due to adverse events. Two of these 10 patients also had grade 3/4 total bilirubin elevations, but no patient experienced hepatic decompensation. Eight of the 10 patients who discontinued due to ALT/AST elevations (80%) subsequently achieved SVR. For the 16 patients who had grade 3/4 ALT elevations on-treatment, the median time to elevation was ~10 weeks (range 4 to 23 weeks), with rapid reversal in ~2.5 weeks after discontinuation. Most patients with baseline ALT and AST elevations experienced rapid improvement during the first 2 to 4 weeks of treatment, including all patients with grade 3/4 elevations at baseline, with mean decreases at 4 weeks of 43.7 U/L and 35.1 U/L, respectively.

Discussion

Treatment with interferon-based therapy is not an option for many patients with chronic HCV. The findings from this phase 3 study evaluating interferon-free, ribavirin-free, all-oral treatment with daclatasvir and asunaprevir demonstrated high rates of SVR in Japanese patients infected with HCV genotype 1b. Both interferon-ineligible/intolerant and previously treated nonresponder patient groups experienced a rapid reduction in HCV RNA by week 2. The primary endpoint, SVR_{24}, was achieved in 87.4% of patients who were ineligible or intolerant to interferon-based therapies and in 80.5% of patients who had not responded to treatment previously. These high rates of SVR obtained with daclatasvir and asunaprevir represent a significant improvement of cure rates in patient populations typically associated with poor responses to other therapies or with limited therapeutic options. Other factors typically associated with a poor response to therapy, including male gender, high baseline HCV RNA, advanced age, non-CC *IL28B* genotype, and cirrhosis, did not appear to impact response rates, although the number of patients in these subgroups was small.

The response rates in this study were higher than those observed in a phase 3 study evaluating triple therapy with telaprevir and peginterferon/ribavirin in Japanese patients infected with HCV genotype 1 with no response to prior treatment. The SVR rate of nonresponder patients in that study was 34.4%, and safety issues included anemia, severe rash, renal toxicity, and gastrointestinal-related disorders.[7] In a global phase 3 trial, SVR rates ranged from 54% to 59% in partial-responder and 29% to 33% in null-responder patients receiving telaprevir combined with peginterferon/ribavirin.[4] Simeprevir in combination with peginterferon/ribavirin achieved an SVR rate of 38-51% in Japanese nonresponder patients. In the present study, partial-responder and null-responder patients achieved better outcomes (77.8% and 81.3%, respectively), with a much more favorable safety profile. The response rate observed in the ineligible/intolerant group in this study was also notable, especially when considering these patients had no option for curative treatment.

This study was limited to Japanese patients; an ongoing phase 3 study in a similar patient population in the U.S. and Europe will determine whether region-related differences in patient characteristics influence outcomes with this regimen. The results from this phase 3 trial are consistent with the results of a small phase 2a study of Japanese patients treated with daclatasvir and asunaprevir; SVR rates were 64% in peginterferon/ribavirin-ineligible or intolerant patients and 91% in null responder patients.[15] A phase 2b trial combining NS3 (faldaprevir) and NS5B (deleobuvir) inhibitors showed only a 57% SVR in previously untreated patients with HCV genotype-1b infection.[16] In addition, other all-oral regimens earlier in clinical development may provide greater efficacy: in a phase 2

study, SVR rates of 95% to 100% were achieved in treatment-naïve and experienced genotype 1-infected patients treated with sofosbuvir (NS5B inhibitor) in combination with ledipasvir (NS5A inhibitor), with or without ribavirin.[17] The more complex combination of NS3 (ABT-450, plus ritonavir to improve drug exposure), NS5A (ABT-267), and NS5B (ABT-333) inhibitors, with or without ribavirin, achieved SVR rates of 88-96% in treatment-naïve patients and prior null responders with genotype 1 infection. Recent press reports indicate similar results in phase 3 studies with both of these regimens, although full study details are not yet available.[19,20] The combination of daclatasvir and sofosbuvir achieved SVR rates of 88-100% in treatment-naïve patients with genotype 1, 2, or 3 infection, and 95-100% in treatment-experienced patients with genotype 1 infection.[21] However, none of these studies involved patient populations directly comparable to those reported in the present study. Previous experience with HCV regimens indicates that both treatment eligibility and outcomes can vary in relation to variables such as disease stage, patient ethnicity, concomitant medical conditions, and other factors.[3] Further studies of all-oral combinations may provide the evidence needed for optimizing regimen selection on the basis of virologic and patient characteristics.

Response rates at on-treatment week 4 were somewhat higher in the ineligible/intolerant group than in prior nonresponders (84.4% versus 60.9%), but this difference diminished as treatment continued. The early difference in response rates may reflect a reduced contribution of endogenous interferon response in prior nonresponders; the ultimate achievement of an 80.5% SVR rate in this group suggests that such nonresponsiveness can be largely overcome with a potent antiviral regimen.

All-oral treatment with daclatasvir and asunaprevir generally suppressed the enrichment/selection of NS5A and NS3 resistance-associated variants. Virologic failure occurred in 17 patients in each group. Both NS5A and NS3 resistance-associated variants were detected in most patients with virologic failure. There was no apparent association between preexisting NS3 resistance-associated polymorphisms and subsequent virologic outcome. Although more patients with NS5A L31M/V and/or Y93H resistance-associated variants experienced virologic failure, 15/37 of patients with these baseline variants achieved SVR. Thus, pretreatment resistance-associated variants were not absolutely predictive of virologic outcome. Moreover, factors other than resistance, such as lower drug exposure and suboptimal compliance to treatment, likely contributed to treatment failure. The patients with daclatasvir and asunaprevir trough plasma concentrations below median values appeared to be at increased risk of virologic failure (Supporting Fig. 1). Given that patients with $\geq$95% compliance had an SVR_{24} rate of 92.7%, the maintenance of higher compliance is essential for optimizing treatment outcomes.

The rate of premature discontinuation of treatment with daclatasvir and asunaprevir due to adverse events was low. Despite early discontinuation that occurred between weeks 4 and 23, 8 of the 10 patients who discontinued because of elevated levels of ALT and AST achieved SVR_{24}, with rapid reversal of transaminase elevations posttreatment. Although small in number, six patients who achieved SVR were on treatment for 12 weeks or less, suggesting that a shorter treatment period may be possible in some patients. Additionally, baseline elevations of ALT and AST corrected rapidly in most patients after 2 to 4 weeks on treatment, as would be expected with the rapid reduction in HCV RNA levels. The rate of serious adverse events was low and varied among patients, with no consistent pattern of events. The frequency of adverse events was also low, especially compared with historical data in patients receiving a triple regimen with telaprevir and peginterferon/ribavirin that showed a high rate of anemia (91%), pyrexia (85%), and skin disorders (82%).[7]

In conclusion, our findings suggest that 24-week treatment with daclatasvir and asunaprevir provides a highly effective option for patients who currently have no effective treatment options (ineligible or intolerant to interferon-based therapy) and for those patients who did not achieve SVR with prior treatment.

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Contributors: HK, EH, HI, AD, and HM designed the study; EH was the medical lead. HK, YS, KI, JT, YKar, KC, YKaw, AI, KY, KT, NI, KK, TT, NK, and MK recruited patients and obtained the data. HM, HI, EH, and AD analyzed the data. TE and FM provided pharmacokinetic and resistance analyses, respectively. HK, YS, KI, JT, YKar, KC, YKaw, AI, KY, KT, NI, KK, TT, NK, MS, HM, TE, FM, AD,

HI, and EH interpreted study findings. All authors participated in writing the report.

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The Patient-Related Burden of Pegylated-Interferon-α Therapy and Adverse Events among Patients with Viral Hepatitis C in Japan

Hiromitsu Kumada, MD[1], *Marco daCosta DiBonaventura, PhD*[2,*], *Yong Yuan, PhD*[3], *Anupama Kalsekar, MS*[3], *Lewis Kopenhafer, BS*[2], *Ann Tang, PhD*[4], *Timothy W. Victor, PhD*[2], *Gilbert L'Italien, PhD*[3,5], *Kazuaki Chayama, MD, PhD*[6], *Joji Toyota, MD, PhD*[7]

[1]*Department of Hepatology, Toranomon Hospital, Tokyo, Japan;* [2]*Health Outcomes Practice, Kantar Health, New York, NY, USA;* [3]*Global Health Economics and Outcomes Research, Bristol-Myers Squibb, Lawrenceville, NJ, USA;* [4]*Health Economics and Outcomes Research, Bristol-Myers K.K., Tokyo, Japan;* [5]*Yale University School of Medicine, New Haven, CT, USA;* [6]*Department of Gastroenterology and Metabolism, Hiroshima University, Hiroshima, Japan;* [7]*Department of Hepatology, Hokkaido P.W.F.A.C Sapporo-Kosei General Hospital, Sapporo, Japan*

ABSTRACT

Objectives: Pegylated-interferon-α (IFN-α)-based therapies for viral hepatitis C (HCV) are effective, but they are associated with several adverse events (AEs). The primary objectives of this study were to quantify the burden of IFN-α–based treatment and to measure the prevalence and burden of IFN-α–related AEs in Japan. **Methods:** A cross-sectional survey was administered online to patients with HCV in 2013. Patients who were currently taking IFN-α–based therapy (n = 188) were compared with patients who were taking a liver protectant but not IFN-α–based therapy (n = 180) and with patients who were untreated (n = 365) on measures of health-related quality of life (using the Hepatitis Quality of Life Questionnaire, version 2), work productivity, and health care resource use, controlling for sociodemographic characteristics and health history. Among patients taking IFN-α–based therapy, the prevalence and burden of AEs was examined on the same set of health outcomes as noted above along with treatment satisfaction and adherence. **Results:** Compared with untreated patients, patients using IFN-α reported poorer health-related quality of life (physical component summary score, 50.13 vs. 52.04; mental component summary score, 44.12 vs. 47.97), more overall work impairment (32.73 vs. 25.64), more physician visits in the past 6 months (14.51 vs. 8.36), and an increased likelihood of an emergency room visit (odds ratio = 7.25) and hospitalization (odds ratio = 4.05) (all $P < 0.05$). The mean number of AEs was 6.05 for patients using IFN-α. All AEs were associated with poorer health outcomes (particularly the mental component summary score), and most were also associated with lower treatment satisfaction and medication adherence. **Conclusions:** A significant patient burden for IFN-α treatment itself and various AEs was observed. The results suggest that effective, non-IFN-α–based treatments may reduce the societal burden.

Keywords: adherence, adverse events, hepatitis C, interferon, quality of life, resource use, satisfaction, work impairment.

Introduction

Hepatitis C virus (HCV) affects an estimated 170 million people globally and 2 million people in Japan [1]. Partly because of the use of nondisposable syringes for immunizations in the 1950s, which resulted in widespread infection, the prevalence of HCV in Japan peaks among those aged 60 to 70 years [2–4]. In a recent study of voluntary blood donors, 7% of those 70 years or older were infected with HCV [5]. Among symptomatic patients, 60% to 80% will develop chronic infection, which leads to an increased risk of cirrhosis, hepatocellular carcinoma, and end-stage liver disease [6]. Indeed, the prevalence of hepatocellular carcinoma in Japan has increased over the past 50 years, with more than 300,000 patients dying each year; it is estimated that HCV is related to 70% to 90% of these cases [3,7].

Pegylated interferon-α (IFN-α) plus ribavirin (RBV) combination therapy has been the mainstay of HCV treatment. Forty-eight and 24 weeks of IFN-α + RBV treatment for genotypes 1 and 2, respectively, have resulted in a sustained virologic response for approximately 50% and 80% of patients, respectively [8]. The success rate of HCV therapy is expected to improve following the recent approval of telaprevir (TVR), a

Conflict of interest: YY, AK, AT, and GL were full-time employees of Bristol-Myers Squibb (the study sponsor) at the time of this study. MDD, LK, and TWV were employees of Kantar Health (who received research funding from Bristol-Myers Squibb) at the time of the study. HK, KC, and JT received honoraria from Bristol-Myers Squibb K. K. for various presentations.

* *Address correspondence to:* Marco daCosta DiBonaventura, Health Outcomes Practice, Kantar Health, 11 Madison Avenue, 12th Floor, New York, NY 10010.

E-mail: marco.dibonaventura@kantarhealth.com

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new direct-acting antiviral medication (boceprevir, another recently approved direct-acting antiviral, has not been approved for use in Japan). TVR is used in combination with IFN-α + RBV (i.e., IFN-α + RBV + TVR; "triple therapy"), resulting in sustained virologic response rates of approximately 70% among treatment-naive patients and is now considered the new standard of care [7,8]. A significant disadvantage of IFN-α–based therapy (with or without TVR), however, is its poor safety and tolerability profile. Adverse events (AEs) include induced bone marrow depression, flu-like symptoms (e.g., fever, chills, headaches, arthralgia, and myalgia), neuropsychiatric disorders (e.g., severe fatigue, irritability, and apathy), neurological side effects (e.g., seizures, parathesias, confusion, aphasia, cortical blindness, delirium, and extrapyramidal syndromes marked by ataxia and akathisia), and autoimmune syndromes (e.g., autoimmune thyroiditis and diabetes) [9–12]. Among patients using triple therapy, 70% experienced anemia and 80% developed a rash [7].

IFN-α–related AEs have been shown to compromise health-related quality of life and result in dose modifications or discontinuation [13,14]. In a multinational study by Ware et al. [15], the health-related quality-of-life scores of all patients decreased during IFN-α treatment and returned to pretreatment levels during the 24 weeks after treatment. In another study, compared with untreated patients with HCV, those treated with IFN-α showed decrements in energy, physical mobility, and pain based on the Nottingham Health Profile questionnaire [16]. In examining health-related quality of life and IFN-α treatment, Dan et al. [17] found that depression was the most consistent predictor of health-related quality of life in patients. IFN-α treatment also negatively impacts work productivity. Brook et al. [18] examined the impact of HCV treatment with IFN-α and/or RBV on absenteeism and work productivity using longitudinal data from the Human Capital Management Services Research Reference Database. Treated employees had 0.52 more health-related work absence days than did untreated employees (1.27 vs. 0.75 workdays monthly) and incurred significantly greater expenditures for sick leave and short-term disability [18].

In sum, research has demonstrated that existing IFN-α–based therapies including triple therapy are effective, but they are also associated with various AEs. The impact of current IFN-α treatment on patient burden is of particular importance in Japan where the predominantly older patient population may be even less likely to tolerate IFN-α–based treatment [13]. To date, there is a lack of research examining the patient-reported treatment-related burden of HCV in Japan. Thus, the primary objectives of this study were to quantify the humanistic and economic burden of IFN-α–based treatment and to measure the prevalence and burden of IFN-α–related AEs.

Methods

Data Source

The current study includes data from a 2013 online survey that was administered to respondents of the Japan National Health and Wellness Survey (NHWS). The NHWS is an annual general health survey that includes questions on medical conditions, symptoms, treatment information, and health outcomes among other variables (N = 30,000 per year). Respondents to the Japan NHWS were recruited from an online panel using a stratified random sample framework (with quotas based on sex and age) to match the characteristics of the adult population in Japan. Comparisons between the Japan NHWS and governmental sources are reported elsewhere [19]. To enhance sample sizes, particularly of the IFN-α–treated population, members of the same online panel that serves as the sample source for the Japan NHWS were also contacted directly to participate. All respondents who completed the survey were compensated in the form of points, which could be exchanged for small items or used to enter into a raffle for larger prizes. Although there is no specific monetary value to these points, it would approximate to less than US $10. The protocol was reviewed and approved by an institutional review board, and all respondents provided informed consent.

Study Sample

Respondents who reported a diagnosis of HCV and were 20 years or older were eligible for this study; respondents who reported taking an IFN-α–based therapy but were not able to report the specific form of IFN-based therapy (i.e., IFN-α alone, IFN-α + RBV, or IFN-α + RBV + TVR; as mentioned above, triple therapy including boceprevir was not included in this study because boceprevir is not approved for use in Japan) were excluded. A total of 733 patients diagnosed with HCV (365 who were untreated, 188 using IFN-α–based therapy, and 180 using liver protectants, a common treatment for HCV in Japan) met all inclusion and exclusion criteria and completed the survey. Liver protectants (e.g., ursodeoxycholic acid and glycrrhizin) are prescriptive palliative remedies common in Japan, which are used as treatments to improve liver dysfunction for those who are IFN-α intolerable or who choose not to receive IFN-α therapies. A priori minimums were set for each of these groups to ensure sufficient statistical power for comparisons (i.e., 350 untreated, 150 IFN-α–based therapy, 175 liver protectants), and so these sample sizes were not intended to provide information on the natural prevalence of these groups.

Study Measures

Treatment usage

Respondents were categorized on the basis of whether they were currently using an IFN-α–based therapy regardless of any other treatments, liver protectants, or whether they were untreated.

Patient characteristics

All respondents provided data on sex, age, education, annual household income, general health history (smoking behavior, exercise behavior, height and weight [which was converted into a body mass index category], and comorbidities using the Charlson comorbidity index [CCI] [20]), and HCV disease history (years diagnosed, genotype, viral load).

Adverse events

AEs were assessed only among respondents using IFN-α–based therapy ("Some people who take prescription hepatitis C medication experience side effects as a result of the medication. To what degree do you experience each of the following side effects when you take [IFN-α alone, IFN-α + RBV, or IFN-α + RBV + TVR depending upon the patient's current regiment]?"). Patients then rated the following AEs as either "none," "mild," "moderate," "severe," and "very severe": fatigue, flu-like symptoms, depression, dyspnea, muscle weakness, anemia, headache, skin rash, nausea, dysgeusia, and insomnia. Only the presence (a rating of "mild" to "very severe") versus absence (a rating of "none") of each AE was considered in this study.

Quality of life

The Hepatitis Quality of Life Questionnaire (HQLQ), version 2 (HQLQv2), was used to assess both generic and disease-specific elements of quality of life [21]. The HQLQ includes the Short

Form-36 version 2 items (which can be used to assess generic aspects of health status) as well as additional hepatitis-related items. Specifically, there are two generic health summary scores (physical component summary [PCS] and mental component summary [MCS] scores), eight generic health domain scores (bodily pain, vitality, physical functioning, physical role limitations, general health, mental health, social functioning, and emotional role limitations), and four hepatitis-specific health domain scores (health distress, positive well-being, hepatitis distress, and hepatitis limitations). For all summary and domain scores, higher scores indicate greater quality of life. For generic summary and domain scores, differences between groups of 3 and 5 points, respectively, represent clinically meaningful differences [22]. No well-established standard for clinically meaningful differences currently exists for hepatitis-specific domain scores.

Work productivity

Work productivity and impairment was assessed using the Work Productivity and Activity Impairment questionnaire [23]. Four subscales (absenteeism, presenteeism, overall works impairment, and activity impairment) are generated in the form of percentages, with higher values indicating greater impairment. Although only those patients currently employed will have data on absenteeism, presenteeism, and overall work impairment, all patients have data on activity impairment.

Resource use

Health care utilization was defined by the number of health care provider visits, the presence of an emergency room (ER) visit, and the presence of a hospitalization. All events, which were total events and not specific to HCV, were recalled on the basis of the past 6 months.

Medication satisfaction

The Treatment Satisfaction Questionnaire for Medication, version 2, was used to assess satisfaction with hepatitis medications [24]. This 11-item instrument includes four subscales: effectiveness, tolerability, convenience, and global satisfaction.

Medication adherence

Medication adherence was assessed using the eight-item version of the Morisky Medication Adherence Scale (MMAS-8) [25]. Adapted specifically for HCV treatments, the MMAS-8 assess the degree to which patients have been adherent with their medications. A total score is categorized into low, medium, and high adherence.

Statistical Analyses

Demographic and health history variables were compared among respondents who were currently using an IFN-α–based therapy, using liver protectants, or who were untreated. Differences were examined using chi-square tests and one-way analyses of variance (the latter were used regardless of whether there were two or three analysis groups to compare).

Two separate comparisons were made to examine the burden of IFN-α treatment. First, patients currently using IFN-α (n = 188) were compared with all other patients not using IFN-α (n = 545; including those who were currently using a liver protectant). Second, patients using IFN-α (n = 188) were also compared with only those patients who were untreated (n = 365). Both comparisons were made with respect to the MCS and PCS scores and all four hepatitis-specific domains from the HQLQv2 using general linear models, all measures of the Work Productivity and Activity Impairment and the number of physician visits using generalized linear models (specifying a negative binomial distribution and a log-link function), and ER visits and hospitalizations using logistic regressions. All models adjusted for age, sex, and the CCI. Adjusted means from these models were produced and compared on the basis of the significance of the treatment group variable in the regression model.

The burden of individual AEs was examined only among those using IFN-α–based treatment by comparing those with a given AE versus those without a given AE. All comparisons were made with respect to MCS and PCS scores and all four hepatitis-specific domains from the HQLQv2 using general linear models, all measures of the Work Productivity and Activity Impairment and the number of physician visits using generalized linear models (specifying a negative binomial distribution and a log-link function), and ER visits and hospitalizations using logistic regressions. All models adjusted for age, sex, and the CCI. Adjusted means from these models were produced and compared on the basis of the significance of the AE variable in the regression model. In addition, differences in treatment satisfaction (all four subscales of the Treatment Satisfaction Questionnaire for Medication, version 2) and adherence scores (low vs. medium vs. high levels of adherence according to the MMAS-8) were examined as a function of the presence versus absence of each individual AE.

Analyses were conducted in SASv9.2; the cutoff for statistical significance was a priori set at $P < 0.05$.

Results

Sample Demographic Characteristics and Health History

A total of 188 (25.65%) respondents were currently using an IFN-α–based therapy, 180 (24.56%) respondents were currently using a liver protectant without IFN-α–based therapy, and the remaining 365 (49.80%) respondents were not currently treated. Across the sample, most respondents were men (68.76%) with a mean age of 55.02 ± 10.86 years (Table 1). Nearly a fifth (18.28%) of all respondents were elderly (i.e., 65 years old or older). This did vary significantly by treatment group as current patients using IFN-α were the youngest (mean = 51.79 years old; 12.77% elderly) followed by those untreated (mean = 55.01 years old; 16.99% elderly) followed by liver protectant users (mean = 58.43 years old; 26.67% elderly). Even despite the negative skewness of the age distribution, the majority (62.48%) of the patients were currently employed.

The CCI was highest among patients using IFN-α (mean = 1.13) compared with those using liver protectants (mean = 0.77) and untreated patients (mean = 0.62). Patients on liver protectants were significantly more likely to report long-term complications of HCV infection such as cirrhosis (20.56% including compensated, decompensated, and unknown cirrhosis vs. 7.45% and 4.66% for patients using IFN-α and those untreated, respectively) and hepatocellular carcinoma (8.89% vs. 3.19% and 3.56% for patients using IFN-α and those untreated, respectively) (both $P < .05$).

Effect of IFN-α–Based Therapy on Health-Related Quality of Life, Work Impairment, and Health Care Resource Use

Adjusting for confounding variables, patients using IFN-α–based therapy reported significantly lower levels of PCS and MCS, the latter of which exceeded the threshold for a clinically relevant effect, as well as lower health distress, hepatitis limitations, and hepatitis distress (see Table 2). No differences were observed with respect to positive well-being. Patients using IFN-α–based therapy also reported significantly greater overall work impairment and physician visits in the past 6 months than did those who were

Table 1 – Sociodemographic characteristics and health history differences among treatment groups.

	Total (N = 733)	IFN-α (N = 188)	Liver protectant (N = 180)	Untreated (N = 365)	P
Male, n (%)	504 (68.76)	136 (72.34)	139 (77.22)	229 (62.74)	0.001
Age (y), mean ± SD	55.02 ± 10.86	51.79 ± 12.68	58.43 ± 9.54	55.01 ± 9.94	<0.001
Age group (y), n (%)					<0.001
<40	59 (8.05)	29 (15.43)	5 (2.78)	25 (6.85)	
40–49	147 (20.05)	36 (19.15)	28 (15.56)	83 (22.74)	
50–59	263 (35.88)	70 (37.23)	60 (33.33)	133 (36.44)	
60–69	198 (27.01)	40 (21.28)	64 (35.56)	94 (25.75)	
70+	66 (9.00)	13 (6.91)	23 (12.78)	30 (8.22)	
Education, n (%)					0.435
Junior high school	28 (3.82)	7 (3.72)	9 (5.00)	12 (3.29)	
High school	239 (32.61)	49 (26.06)	61 (33.89)	129 (35.34)	
2-y college	58 (7.91)	13 (6.91)	15 (8.33)	30 (8.22)	
4-y college	294 (40.11)	84 (44.68)	73 (40.56)	137 (37.53)	
Graduate school	40 (5.46)	14 (7.45)	9 (5.00)	17 (4.66)	
Professional school	74 (10.10)	21 (11.17)	13 (7.22)	40 (10.96)	
Annual household income (¥), n (%)					0.076
<3,000,000	164 (22.37)	30 (15.96)	54 (30.00)	80 (21.92)	
3,000,000–<5,000,000	230 (31.38)	58 (30.85)	49 (27.22)	123 (33.70)	
5,000,000–<8,000,000	163 (22.24)	47 (25.00)	36 (20.00)	80 (21.92)	
8,000,000 or more	129 (17.60)	42 (22.34)	29 (16.11)	58 (15.89)	
Decline to answer	47 (6.41)	11 (5.85)	12 (6.67)	24 (6.58)	
Currently employed, n (%)	458 (62.48)	138 (73.40)	102 (56.67)	218 (59.73)	0.001
Body mass index category, n (%)					0.490
Underweight	56 (7.64)	18 (9.57)	12 (6.67)	26 (7.12)	
Normal weight	504 (68.76)	121 (64.36)	132 (73.33)	251 (68.77)	
Obese	163 (22.24)	47 (25.00)	35 (19.44)	81 (22.19)	
Unknown	10 (1.36)	2 (1.06)	1 (0.56)	7 (1.92)	
Exercised in past month, n (%)	361 (49.25)	95 (50.53)	95 (52.78)	171 (46.85)	0.394
Alcohol use, n (%)	438 (59.75)	112 (59.57)	81 (45.00)	245 (67.12)	<0.001
Smoking behavior, n (%)					0.001
Current smoker	207 (28.24)	74 (39.36)	39 (21.67)	94 (25.75)	
Former smoker	232 (31.65)	51 (27.13)	67 (37.22)	114 (31.23)	
Never smoked	294 (40.11)	63 (33.51)	74 (41.11)	157 (43.01)	
Charlson comorbidity index	0.79 ± 1.88	1.13 ± 3.16	0.77 ± 1.15	0.62 ± 1.11	0.009

IFN, interferon.

untreated. In addition, the odds of visiting the ER and being hospitalized for patients using IFN-α–based therapy were more than four times that of untreated patients. Similar effects were observed when comparing patients using IFN-α–based therapy and all those not using IFN-α–based therapy; however, overall work impairment and the number of physician visits were not significantly different (32.55% vs. 26.36% and 14.68 vs. 11.77, respectively).

Table 2 – Summary of adjusted effects between those with and without IFN-α–based therapy.

Outcome	IFN-α– based therapy	No IFN-α–based therapy	IFN-α–based therapy	Untreated
Physical component summary	50.158*	51.547	50.126*	52.036
Mental component summary	44.309*	47.400	44.121*	47.969
Health distress	66.500*	72.446	66.333*	74.560
Positive well-being	48.351	48.385	48.739	47.157
Hepatitis limitations	68.457*	82.257	68.392*	84.207
Hepatitis distress	73.147*	83.052	72.895*	86.646
Overall work impairment, %	32.554	26.358	32.729*	25.643
Activity impairment, %	30.447*	24.835	30.759*	23.745
Number of physician visits	14.679	11.769	14.506*	8.363
ER visit (≥1) (odds ratio)	4.635*		7.246*	
Hospitalization (≥1) (odds ratio)	2.780*		4.052*	

ER, emergency room; IFN, interferon.
* $P < 0.05$ relative to those without IFN-α–based therapy/untreated.

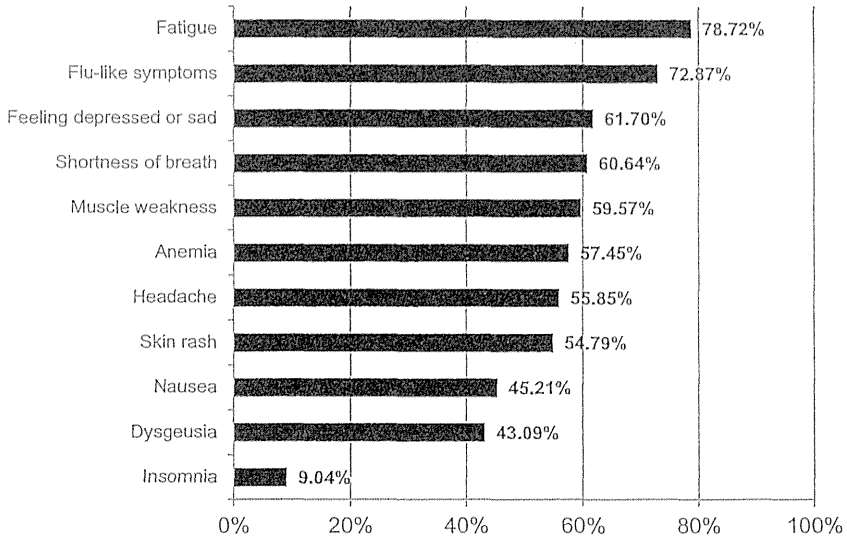

Fig. 1 – Prevalence of AEs reported by patients using IFN-α (N = 188). AE, adverse events; IFN-α, Pegylated-Interferon-α.

Prevalence of Adverse Events

The mean number of AEs per patient on IFN-α–based therapy was 6.05 ± 3.33. In order of prevalence, the AEs reported by at least half of the patients included fatigue (79%), flu-like symptoms (73%), depression/sadness (62%), dyspnea (62%), muscle weakness (60%), anemia (57%), headache (56%), and skin rash (55%) (see Fig. 1).

Effect of AEs on Health-Related Quality of Life, Work Impairment, and Health Care Resource Use

For each AE, those who experienced the event and those who did not were compared with respect to health outcomes adjusting for confounding variables (see Table 3). With the exception of anemia, all AEs were associated with significant decrements in the PCS score. Clinically relevant differences were observed

Table 3 – Adjusted health-related quality-of-life differences between those with and without AEs.

AEs	Generic quality-of-life summary scores		Hepatitis-specific domains			
	Physical component summary	Mental component summary	Health distress	Positive well-being	Hepatitis limitations	Hepatitis distress
Anemia	49.333	41.881*	60.438*	49.572	61.672*	66.544*
No anemia	50.481	45.320	69.033	47.953	73.659	77.603
Fatigue	48.980*	41.955*	59.431*	50.166	63.588*	67.728*
No fatigue	52.935	48.486	81.356	44.135	78.558	84.28
Depression	48.974*	39.866*	54.661*	51.652	59.473*	62.631*
No depression	51.187	48.949	79.296	44.423	78.534	85.135
Skin rash	48.360*	40.093*	53.981*	52.57*	58.355*	61.703*
No skin rash	51.592	47.284	76.352	44.415	76.974	82.819
Flu-like symptoms	48.946*	41.795*	59.351*	51.121	62.717*	66.603*
No flu-like symptoms	52.171	47.505	76.843	42.871	77.668	83.734
Dyspnea	48.098*	40.577*	56.54*	52.114*	61.072*	64.466*
No dyspnea	52.475	47.607	75.736	43.905	75.556	81.701
Muscle weakness	48.214*	40.056*	54.461*	52.526*	57.841*	62.52*
No muscle weakness	52.189	48.190	78.295	43.515	79.937	84.115
Headache	48.214*	39.715*	54.649*	53.972*	59.618*	61.15*
No headache	51.854	47.935	76.047	42.445	75.825	84.027

Note. All models adjusted for age, sex, and comorbidities.
AE, adverse events.
* $P < 0.05$ relative to those without AEs.

Table 4 – Adjusted work impairment and healthcare resource use differences between those with and without AEs.

AEs	Adjusted means		Odds ratios	
	Overall work impairment	Physician visits	ER visit	Hospitalization
Anemia	36.207	17.446*	1.42	4.23*
No anemia	30.048	11.084		
Fatigue	38.862*	16.743*	1.45	5.75*
No fatigue	19.518	7.293		
Depression	44.694*	15.488	1.12	1.07
No depression	19.035	13.488		
Skin rash	42.363*	18.417*	2.66*	2.49*
No skin rash	22.993	10.274		
Flu-like symptoms	38.525*	17.370*	0.88	4.41*
No flu-like symptoms	23.434	7.702		
Dyspnea	42.270*	19.190*	2.44	5.84*
No dyspnea	22.380	7.995		
Muscle weakness	42.074*	18.439*	3.70*	2.49*
No muscle weakness	23.025	9.255		
Headache	43.844*	19.031*	0.88	3.50*
No headache	21.205	9.516		

Note. All models adjusted for age, sex, and comorbidities.
AE, adverse events; ER, emergency room.
* $P < 0.05$ relative to those without AEs.

with respect to fatigue (48.98 vs. 52.94), skin rash (48.36 vs. 51.59), flu-like symptoms (48.95 vs. 52.17), dyspnea (48.10 vs. 52.48), muscle weakness (48.21 vs. 52.19), and headache (48.21 vs. 51.85) (all $P < 0.05$). All AEs were associated with significant and clinically relevant decrements in the MCS score (all $P < .05$). The largest effects were observed for depression (39.87 vs. 48.95), headache (39.72 vs. 47.94), and muscle weakness (40.06 vs. 48.19) (all $P < 0.05$).

AEs were also significantly associated with decrements in hepatitis-specific domains (see Table 3). Interestingly, no AE was associated with poorer positive well-being and, in fact, for skin rash, dyspnea, muscle weakness, and headache, the presence of the AE was associated with higher positive well-being (though scores for all groups were quite low, <54 on a 0–100 scale). The remaining subscales had the expected pattern of lower scores among those who reported an AE. Aside from anemia, all other AEs were associated with comparable decrements in health distress (between 17.49 and 24.64 points lower; all $P < 0.05$). Both hepatitis limitations and hepatitis distress were significantly lower among those with each individual AE; patients reporting depression, skin rash, and muscle weakness reported the largest decrements in these domain scores.

Among patients using IFN-α–based therapy and who were employed, the presence of all AEs (with the exception of anemia) was associated with significantly higher overall work impairment (see Table 4). Indeed, the level of work impairment was approximately double for those reporting each AE and, in absolute levels, represented 40% of the work time that was missed or rendered ineffective because of health. A greater number of physician visits were also reported for all those with AEs, often more than double the number of visits without AEs, with the exception of depression, which was not significant. Only skin rash (odds ratio = 2.66, $P < 0.05$) and muscle weakness (odds ratio = 3.70, $P < 0.05$) were associated with an increased likelihood of an ER visit. All AEs, with the exception of depression, were associated with an increased likelihood of a hospitalization (all $P < 0.05$).

Adherence and Satisfaction with and Without AEs

The presence of AEs was also significantly associated with decreased medication satisfaction and adherence (see Table 5). Nausea (48.92 vs. 65.05, $P < 0.05$), fatigue (54.34 vs. 70.42, $P < 0.05$), and skin rash (51.05 vs. 65.88, $P < 0.05$) were most strongly related with decrements in global satisfaction though all other AEs were also associated with lower scores with the exception of anemia (55.94 vs. 60.21, P = nonsignificant) and, as previously discussed, insomnia (59.31 vs. 57.60, P = nonsignificant). Several AEs were also significantly related to a reduced probability of having high levels of adherence: depression (25.86% vs. 48.61%, $P < 0.05$), flu-like symptoms (28.47% vs. 50.98%, $P < 0.05$), skin rash (25.24% vs. 45.88%, $P < 0.05$), fatigue (30.41% vs. 50.00%, $P < 0.05$), nausea (24.71% vs.42.72%, $P < 0.05$), and headache (26.67% vs. 44.58%, $P < 0.05$).

Discussion

The overall objective of this study was to quantify the patient-reported burden of IFN-α treatments and AEs among patients in Japan. This investigation is particularly relevant for Japan given the aging HCV population who may be even less likely to tolerate the various AEs of IFN-α therapy [13]. Consistent with previous studies in which patients with HCV in Japan were 10 to 15 years older than patients with HCV in the United States [26–28], approximately a fifth of our sample was 65 years or older. The age distribution was slightly younger than in recent studies [29] and may reflect differences in the sampling method.

As might be expected, only 12.77% of the patients currently using IFN-α were elderly, suggesting that the burden of IFN-α may be altering prescribing patterns. Interestingly, the IFN-α group (although the youngest) was also the most saddled with comorbidities. Although more extensive research would be required, it is possible that age is a more important deterrent to administering IFN-α than comorbidities themselves. Indeed, Iwasaki et al. [13] concluded that age was an important factor in the safety of IFN-α

Table 5 – Relationships between AEs and side effects and treatment satisfaction.

	TSQM: Side effects subscale*	TSQM: Effectiveness subscale	TSQM: Convenience subscale	TSQM: Global satisfaction subscale	MMAS: Total score (%)			
	Mean	Mean	Mean	Mean	Low adherence	Medium adherence	High adherence	P
Anemia (n = 108)	46.37	52.47†	52.62†	55.94	29.63	41.67	28.70	0.111
No anemia (n = 80)	55.75	62.29	60.14	60.21	20.00	37.50	42.50	
Fatigue (n = 148)	47.46†	53.15†	52.67†	54.34†	29.05	40.54	30.41	0.031
No fatigue (n = 40)	68.75	69.58	67.50	70.42	12.50	37.50	50.00	
Depression (n = 116)	40.44†	51.58†	50.19†	52.95†	34.48	39.66	25.86	<0.001
No depression (n = 72)	69.87	64.81	64.89	65.51	11.11	40.28	48.61	
Skin rash (n = 103)	45.29†	48.46†	50.70†	51.05†	30.10	44.66	25.24	0.012
No skin rash (n = 85)	57.94	66.57	62.03	65.88	20.00	34.12	45.88	
Flu-like symptoms (n = 137)	45.79†	52.25†	52.19†	54.68†	29.20	42.34	28.47	0.012
No flu-like symptoms (n = 51)	67.05	68.46	65.58	66.01	15.69	33.33	50.98	
Dyspnea (n = 114)	44.22†	50.00†	51.22†	52.92†	25.44	43.86	30.70	0.301
No dyspnea (n = 74)	61.32	66.89	62.91	65.2	25.68	33.78	40.54	
Muscle weakness (n = 112)	43.26†	50.07†	50.45†	53.05†	30.36	38.39	31.25	0.168
No muscle weakness (n = 76)	64.04	66.34	63.74	64.69	18.42	42.11	39.47	
Headache (n = 105)	44.44†	49.84†	50.53†	52.22†	33.33	40.00	26.67	0.007
No headache (n = 83)	58.33	65.26	62.52	64.76	15.66	39.76	44.58	
Nausea (n = 85)	39.05†	46.67†	47.65†	48.92†	36.47	38.82	24.71	0.003
No nausea (n = 103)	61.11	64.89	62.57	65.05	16.50	40.78	42.72	

AE, adverse event; MMAS, Morisky Medication Adherence Scale; TSQM, Treatment Satisfaction Questionnaire for Medication.

* Only among those who reported experiencing side effects within the TSQM instrument (N = 127).

† $P < 0.05$ relative to those without AEs.

combination therapy as older patients experienced more AEs and were more likely to require dose reductions or discontinue therapy.

The results of the current study demonstrate the immense burden of IFN-α treatment across various humanistic and economic domains. In terms of health-related quality of life, patients using IFN-α reported both poorer MCS and PCS scores on the HQLQ relative to those not using IFN-α (i.e., those using liver protectants) and those untreated. Specifically, the clinically relevant burden of IFN-α on mental health was comparable to the burden of nocioceptive pain in Japan [30] and greater than the burden of type 2 diabetes, obesity, and hypertension in Japan [31]. The lack of research examining the health-related quality of life of patients with HCV undergoing IFN-α treatment in Japan does not allow us to compare the current study findings with those of other studies; however, the lower PCS and MCS scores during IFN-α treatment are consistent with previous studies conducted in Western countries [15,32].

Patients using IFN-α treatment reported nearly 30% more work impairment than did untreated patients. Patients using IFN-α also reported more health care resource utilization than did both all other patients not using IFN-α and patients who were untreated. Research studies examining the indirect and direct costs (e.g., work productivity and health care resource use) for treated patients with HCV is scarce, even in Western countries. The handful of studies examining this topic in the United States found evidence of work impairments among patients with HCV treated with IFN-α [18,33,34]. To the best of our knowledge, the current study is the first to demonstrate both work productivity loss and increased health care resource use among patients with HCV treated with IFN-α in Japan. The current study also highlights the importance of factoring in the indirect costs (i.e., work productivity losses) even among an older patient sample when estimating the total societal burden. It should be emphasized that the intent of this analysis was to determine the overall burden of treatment and not the overall effectiveness of these treatments. Better health outcomes, such as higher quality of life, among those using liver protectants and those untreated does not imply that those treatments have superior clinical effectiveness.

The burden of IFN-α is likely attributed to the treatment's various AEs. Indeed, most AEs were reported by more than half the IFN-α subsample with an average of six AEs per patient. Consistent with published studies examining the AEs of IFN-α, the most commonly reported AEs included fatigue, flu-like symptoms, depression/sadness, dyspnea, muscle weakness, anemia, headache, and skin rash [9,35]. Although the burden varied by AE, in all cases there was a significant (and often clinically relevant) association with health-related quality of life, work impairment, and health care resource use events. The burden of AEs on health-related quality of life was particularly strong and more specifically, the mental health–related aspects were generally the most affected as indicated by the largest effect sizes. These results suggest that although AEs can take a physical toll on the patient, their effect on the mental health of the patient may be even more burdensome.

IFN-α–related AEs were also associated with poorer treatment satisfaction and adherence. The effects were among the strongest for depression in that only a quarter of patients with depression reported high adherence compared with nearly half of those without depression. This was consistent with a study conducted by Fried et al. [36] in which 32% to 43% of the patients on IFN-α combination therapy discontinued treatment because of an AE and 22% to 30% did so as a result of depression. These findings on the relationships between AEs with both satisfaction and nonadherence suggest significant unmet needs for IFN-α–based therapy. The lack of adherence to treatment may ultimately contribute to poorer effectiveness because patients discontinue treatment before realizing the benefits [37].

There are important implications for reducing HCV patients' AE burden during treatment. The reduction of AEs during treatment would likely lead to better health-related quality of life and greater treatment adherence, ultimately contributing to an improved likelihood of treatment success. As the current study suggests, AEs are also associated with decrements in work productivity and increases in the use of health care resources, which leads to an economic burden on a societal level. With the health burden of HCV in Japan expected to rise over the next several decades as a result of its aging patient population [7], there is a substantial need for improved treatments with more tolerable profiles.

There are several limitations to the current study that should be noted. The current study was a self-reported survey and there was no clinical verification of HCV diagnosis among patients. The self-reported nature of the study also could have introduced additional measurement error (due to recall bias) into such variables as health care resource utilization or adherence. Future research could overcome this limitation by combining self-reported data with clinical data to accurately capture the measures in question. Given that the survey was conducted via the Internet, the extent to which the sample generalizes to the population is unclear. It is possible that certain HCV subpopulations may have been underrepresented.

Regardless of these limitations, this study also offers several strengths. Only through self-report is it possible to understand health-related quality of life, symptomatic AEs, work impairments, and treatment satisfaction. These constructs are vital for documenting the overall treatment burden and understanding how treatment advances (which, presumably, would reduce the prevalence of AEs) would subsequently affect patient-reported outcomes, adherence, and discontinuation. The current study adds considerably to the literature because no study to our knowledge has examined these constructs in Japan.

Conclusions

The present study suggests that there is a significant patient burden with IFN-α treatment in Japan. This burden is likely explained by highly prevalent AEs, which are each associated with decrements in health-related quality of life, work productivity, and increases in health care resource use. Overall levels of satisfaction and adherence are low and partially explained by the presence of AEs; indeed, discontinuation is often attributed to the presence of AEs. Perhaps as a result, IFN-α therapy is uncommon among the elderly. Collectively, these results suggest that effective, non-IFN-α–based treatment may alleviate a substantial humanistic burden and could be associated with greater rates of patient satisfaction and adherence.

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Long-term efficacy and emergence of multidrug resistance in patients with lamivudine-refractory chronic hepatitis B treated by combination therapy with adefovir plus lamivudine

Fumitaka Suzuki · Tetsuya Hosaka · Yoshiyuki Suzuki · Norio Akuta · Hitomi Sezaki · Tasuku Hara · Yusuke Kawamura · Masahiro Kobayashi · Satoshi Saitoh · Yasuji Arase · Kenji Ikeda · Mariko Kobayashi · Sachiyo Watahiki · Rie Mineta · Hiromitsu Kumada

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Abstract
Background Few studies have investigated the emergence of multidrug resistance to adefovir dipivoxil (ADV) plus lamivudine (LAM) combination therapy for patients with LAM-refractory chronic hepatitis B (CHB). In this retrospective study, we investigated the long-term clinical course of these patients with or without multidrug resistance mutations.
Methods We analyzed 406 Japanese patients with LAM-refractory CHB treated with combination therapy with follow-up for a median of 5.4 (0.5–9.5) years. Multidrug resistance of hepatitis B virus (HBV) DNA was analyzed using direct sequencing or cloning methods at baseline and viral breakthrough or insufficient decline during combination therapy.
Results Ratio of patients with undetectable serum HBV DNA levels (<2.6 log copies/mL) during combination therapy was 63, 72, 75, 79, 82, 80 and 85 % at years 1 through 7, respectively. Substitutions associated with multidrug resistance were identified in 11 patients (2.7 %) at baseline, and in 12 patients (3 %) during therapy. HBV DNA levels of patients with rtA181S mutation at baseline and emergence of rtA181T + rtN236T double mutation or a wide variety of mutations during combination therapy could not be suppressed. Moreover, using ultra-deep sequencing, rtA181T/V mutations were detected at baseline in 7 of 10 patients with emergent multidrug resistance during combination therapy, although 6 of these 7 patients had very low frequency (<1 %) variants.
Conclusion Long-term ADV plus LAM combination therapy is effective in LAM-refractory patients. However, HBV DNA levels of the patients with multidrug resistance at baseline or during combination therapy sometimes could not achieve complete suppression or were re-elevated after a decrease.

Keywords Adefovir dipivoxil · Lamivudine · Hepatitis B virus · Ultra-deep sequence · Multidrug resistance

Abbreviations

HBV	Hepatitis B virus
IFN	Interferon
NA	Nucleoside/nucleotide analogues
LAM	Lamivudine
ADV	Adefovir dipivoxil
ETV	Entecavir
TDF	Tenofovir disoproxil fumarate
CHB	Chronic hepatitis B
HBeAg	Hepatitis B e antigen
ALT	Alanine aminotransferase
HBsAg	Hepatitis B surface antigen
PCR	Polymerase chain reaction
CLEIA	Chemiluminescent enzyme immunoassay
rt	Reverse transcriptase

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F. Suzuki (✉) · T. Hosaka · Y. Suzuki · N. Akuta · H. Sezaki · T. Hara · Y. Kawamura · M. Kobayashi · S. Saitoh · Y. Arase · K. Ikeda · H. Kumada
Department of Hepatology, Toranomon Hospital, 2-2-2 Toranomon, Minato-ku, Tokyo 105-8470, Japan
e-mail: fumitakas@toranomon.gr.jp

F. Suzuki
Okinaka Memorial Institute for Medical Research, Tokyo, Japan

M. Kobayashi · S. Watahiki · R. Mineta
Research Institute for Hepatology, Toranomon Hospital, Tokyo, Japan

VBT Viral breakthrough
AST Aspartate aminotransferase
CI Confidence interval
Pt Patient

Introduction

Hepatitis B virus (HBV) infection is a common disease that can induce a chronic carrier state, and is associated with the risk of developing progressive disease and hepatocellular carcinoma [1]. Interferon (IFN) and several nucleoside/nucleotide analogues (NA) such as lamivudine (LAM), adefovir dipivoxil (ADV), entecavir (ETV), and tenofovir disoproxil fumarate (TDF) are currently approved for treatment of chronic hepatitis B (CHB) in most countries [2–8]. Successful treatment of CHB with clearance of hepatitis B e antigen (HBeAg), reduction in serum HBV DNA levels, and normalization of alanine aminotransferase (ALT) levels are associated with favorable long-term outcomes, independent of the antiviral drug used [9–11].

LAM is effective in suppressing HBV replication, improving transaminase levels and liver histology, and enhancing the rate of loss of HBeAg. A major problem with the long-term use of lamivudine, however, is its potential to induce viral resistance, with associated increases in HBV DNA and serum transaminases [3, 12, 13]. ADV is reportedly effective in suppressing HBV replication and is approved as a standard therapy in LAM-resistant patients in Japan [14, 15]. However, data concerning the long-term efficacy of ADV treatment in LAM-resistant CHB patients remain limited.

Although both experimental and clinical studies have shown that ADV suppresses not only wild-type but also LAM-resistant strains, the potential for ADV-resistance mutation has emerged. Selection of the rtA181V/T or rtN236T mutant was associated with ADV [13, 16]. Moreover, we previously reported that the emergence of ADV-resistant mutations before and during combination therapy for a period of 2 years was rare [17]. However, ADV-resistant mutations emerging before and during combination therapy might be caused by a poor response to therapy. Moreover, long-term clinical and virological data concerning ADV- or ETV-resistant mutations in LAM-resistant CHB patients receiving long-term ADV plus LAM combination therapy are limited.

The aims of this study were to evaluate the long-term efficiency of ADV plus LAM combination therapy based on virological response (VR), HBeAg clearance, and Hepatitis B surface antigen (HBsAg) clearance, and to investigate the emergence of ADV-, ETV-, or TDF-resistant (or multidrug resistant) mutations before and during combination therapy, and the clinical course of these patients.

Patients and methods

Patients

A total of 406 consecutive adult Japanese patients with chronic HBV infection were treated with ADV in addition to ongoing LAM treatment from 2002 at Toranomon Hospital (Table 1). Several of these patients were included in previous reports [14, 15, 17, 18]. Enrollment in this study and the start of ADV treatment were determined by the following criteria. First, an increase in serum HBV DNA levels of ≥1 log copies/mL during LAM treatment compared with the nadir of initial antiviral efficacy on at least two consecutive occasions, or a serum HBV DNA level of ≥5 log copies/mL after 1 year of LAM monotherapy; and second, no history of treatment with other NAs such as ETV or TDF. Exclusion criteria were a serum creatinine level ≥1.2 mg/dL; coinfection with hepatitis C virus or HIV; and history of other liver diseases, such as autoimmune hepatitis, alcoholic liver disease, or metabolic liver disease. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Toranomon Hospital Ethical

Table 1 Characteristics of patients at the commencement of adefovir dipivoxil plus lamivudine combination therapy

Demographic data	
Total number	406
Sex (female/male)	86/320
Age, years (range)	48 (25–78)
Duration of treatment, years (range)	5.4 (0.5–9.5)
History of IFN therapy (+/−)	157/249
Laboratory data	
Aspartate aminotransferase, IU/L (range)	54 (12–1413)
Alanine aminotransferase, IU/L (range)	76 (9–1563)
Bilirubin, mg/dL (range)	0.7 (0.2–15.5)
Albumin, g/dL (range)	3.9 (1.9–4.7)
Platelets, $\times 10^3/\mu L$ (range)	160 (28–452)
Staging of liver histology (CH/LC)	325/81
Serum HBV DNA, log copies/mL (range)	6.7 (<2.6 to >7.6)
HBeAg, positive/negative/unknown	208/193/5
HBV genotype (A/B/C/D/F)	14/25/364/2/1
rtM204 mutant (%)	365 (90 %)

Values are expressed as the median and range in parentheses, or number and percentage in parentheses

IFN interferon, *HBV* hepatitis B virus, *CH* chronic hepatitis, *LC* liver cirrhosis, *HBeAg* hepatitis B e antigen