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Clinical Characteristics and Treatment Outcome of Peginterferon Plus Ribavirin in Patients Infected with Genotype 6 Hepatitis C Virus in Korea: A Multicenter Study

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Background/Aims: Because of the limited geographic distribution, there have been insufficient data regarding hepatitis C virus (HCV) genotype 6 in Korea. This study aimed to investigate the clinical characteristics and available treatment outcomes of patients with genotype 6 HCV in Korea. **Methods:** From 2004 to 2014, data were collected from Korean patients infected with genotype 6 HCV in eight hospitals. **Results:** Thirty-two patients had genotype 6 HCV. The median age was 44 years, and 6c was the most common subtype. The baseline median alanine transaminase level was 88 (21 to 1,019) IU/mL, and the HCV RNA level was 1,405,000 (96,500 to 28,844,529) IU/mL. Twenty-five patients were treated with peginterferon (PEG-IFN) and ribavirin. Three follow-up losses occurred. Additionally, 13 patients attained a sustained virologic response (SVR), seven patients relapsed, and two patients exhibited a null response. The SVR rates were 40% and 75% for the 24- and more than 48-week treatments, respectively, and five of the six patients who achieved a rapid virologic response (RVR) attained a SVR. **Conclusions:** Korean patients infected with genotype 6 HCV are relatively young, and 6c is the most common subtype. When treated with PEG-IFN and ribavirin, the SVR rate was 52%. Similar to other genotypes, a longer duration of treatment and attainment of RVR are important for SVR. **(Gut Liver 2017;11:270-275)**

Key Words: Hepatitis C, chronic; Genotype 6; Peginterferon alfa; Ribavirin

INTRODUCTION

Hepatitis C virus (HCV) is a major leading cause of chronic liver disease including cirrhosis and hepatocellular carcinoma and about 130 to 150 million people globally have chronic hepatitis C (CHC) infection.[1,2] According to the sequencing of HCV isolate, there are seven genotypes and 67 subtypes.[3] While genotype 1, 2, and 3 are more prevalent and found around the world-wide, genotype 4, 5 and 6 are distributed in limited area. Genotype 4 and 5 are mainly distributed in the Middle East and Africa, and 6 in the Southern China and Southeast Asia including Singapore, Laos, Thailand, Vietnam, and Myanmar, where comprises up to 50% of all hepatitis C patients. On the other hand, HCV genotype 6 is rare in Korea where its prevalence is known as about 1%.[4,5]

Since new oral direct-acting-agents (DAA) have been introduced, a treatment paradigm for HCV infection is changing. However, although some clinical trials demonstrated higher sustained virologic response (SVR) achievement in genotype 6 patients using DAA, those data included only small number of patients with genotype 6.[6,7] Moreover, DAA-based regimen is not likely to be available in many countries yet because of countries' or personal socio-economic situations. For these reasons, peginterferon (PEG-IFN) and ribavirin are still affordable treatment regimens in real-world setting.

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This study was conducted to find the clinical characteristics and treatment outcomes in the patients infected with HCV genotype 6 in Korea.

MATERIALS AND METHODS

From April 2004 to December 2014, data of patients infected with genotype 6 were reviewed from one regional hospital and seven hospitals affiliated with medical colleges located in Gyeonggi-Incheon region, South Korea. Among them, seven patients were from the Gyeonggi-Incheon Peginterferon Alpha and Ribavirin Effect in CHC Treatment (KIPECT) study group.[8]

Baseline clinical and virologic characteristics were obtained by retrospective review of medical records. Data collection was performed with an Excel (Microsoft Corp., Redmond, WA, USA)-based case report form by physicians at each individual hospital. The study protocol was approved by the Institutional Review Boards for exemption from the requirement for informed consent at each hospital and was conducted in accordance with the principles of the Declaration of Helsinki.

All patients were Koreans and anti-HCV positive more than 6 months or clinically assessed as a CHC by using laboratory and radiologic findings. HCV genotyping was conducted by the reverse hybridization principle, nested polymerase chain reaction (PCR) was performed with biotinylated primers from the 5′ untranslated region, and the second-round product was genotyped with a second-generation line probe assay (INNO-LiPA HCV II; Innogenetics, Ghent, Belgium) or restriction fragment mass polymorphism (RFMP; Genematrix Inc., Seongnam, Korea), or direct sequencing method as used in each institution. Qualitative HCV RNA, when it performed, was conducted by an RNA PCR and hybrid method, Cobas Amplicor HCV test version 2.0 (Roche Molecular Systems, Branchburg, NJ, USA; detection limit, 50 IU/mL). Quantitative HCV RNA was measured by real-time PCR assay using the Abbott RealTime HCV assay (Abbott Molecular, Des Plaines, IL, USA; lower detection limit 12 IU/mL) or CobasAmpliPrep/CobasTaqMan HCV assay (Roche Molecular Systems, Pleasanton, CA, USA; lower detection limit 15 IU/mL).

When the patients were treated, either PEG-IFN α-2a or PEG-IFN α-2b plus ribavirin were used. The starting dosage and dose modification of PEG-IFN and ribavirin were determined based on the current guidelines suggested by the Korean Association for the Study of the Liver. However, according to the nature of this retrospective study, selection and discontinuation as well as dosing and treatment duration of PEG-IFN and ribavirin were not controlled, but reflected the clinical practice of the attending physicians.

The patients who developed anemia, neutropenia, and/or thrombocytopenia were generally managed with a dose reduction or permanent discontinuation of the PEG-IFN or ribavirin, as per the guidelines provided.

A rapid virological response (RVR) was defined as undetectable serum HCV-RNA at week 4. The complete early virologic response (cEVR) is based on week 12 data and is defined as an undetectable HCV RNA. A partial EVR (pEVR) refers to a 2 $\log_{10}$ or greater decrease from baseline in HCV RNA at week 12, but persistent detectable HCV RNA. End of treatment response (ETR) was defined as undetectable HCV RNA at the end point of treatment. A SVR was defined as undetectable HCV RNA 24 weeks after completion of antiviral therapy maintained throughout the remaining documented follow-up period. Virological relapse was defined as achieving an ETR but subsequently becoming HCV RNA positive after cessation of treatment. An adherence to antiviral therapy was defined as the actual dose administered divided by the total dose first expected.

Comparison of treatment outcome according to the presence of RVR and the treatment duration was performed using two-sided Fisher exact test.

RESULTS

A total of 32 patients were enrolled. Included patients were aged between 34 and 57 (median, 44) years, and 63% were male. No specific risk for CHC was identified but two patients who received tattooing from the same unlicensed person. Three patients showed hepatitis B surface antigen (HBsAg) positive but negative HBV DNA on their serum (Table 1).

Most common subtype was 6c, documented in 26 patients (81%). There were 6a in three patients, mixed 6/6c in two patients, and 6 in one patient, respectively. Baseline median aspartate transaminase level was 80 (24 to 1,123) U/L and alanine transaminase level was 88 (21 to 1,019) U/L, and HCV RNA level was 1,405,000 (96,500 to 28,844,529) IU/mL. Based on laboratory and imaging findings, five patients showed clinical features suggestive liver fibrosis.

Twenty-five treatment-naïve patients were treated with 180 μg of PEG-IFN α-2a or 1.0 to 1.5 μg/kg of PEG-IFN α-2b with 800 to 1,200 mg of ribavirin. Treatment duration was determined by physicians' discretion, and intended treatment duration was ranged 24 to 54 weeks (Table 2).

Overall, SVR was attained in 13 patients (52%). As follow-up loss occurred in three patients, a total of 22 patients conformed to the treatment protocol. Seven patients relapsed and two were null-responders including one who discontinued treatment for no early virologic response.

By treatment durations, four of 10 patients attained SVR following 24 weeks and nine of 12 patients following more than 48 weeks treatment. When excluding three patients who lost follow-up, the treatment outcome was slightly improved according to longer duration of treatment (p=0.192).

RVR was checked in 14 patients. Five of six patients who showed positive RVR had attained SVR whereas four of eight patients without RVR attained SVR. Two patients who did not achieve EVR were nonresponder. In three patients with pEVR,

Table 1. Clinical Characteristics of Patients with Chronic Hepatitis C Genotype 6

No.	Sex/age	Genotyping method	Subtype	Baseline HCV RNA, IU/mL	AST, U/L	ALT, U/L	WBC, /μL	Hb, g/dL	Platelets, $\times 10^3$/μL	Alcohol*, g/day	Remark	US
1	M/45	INNO-LiPA	6a	3,948,730	57	67	5,780	16.5	167	10	-	-
2	M/53	INNO-LiPA	6c	Positive	122	28	5,430	14.0	54	Nil	-	-
3	M/46	RFMP	6a	1,670,000	121	181	4,350	15.7	124	Nil	-	-
4	F/39	RFMP	6a	185,040	46	108	5,720	16.0	126	60	-	-
5	M/54	RFMP	6c	283,400	97	78	3,260	14.0	156	Nil	Diabetes	-
6	M/37	RFMP	6c	7,560,000	78	154	5,840	15.9	224	25	-	-
7	M/35	RFMP	6c	5,170,000	224	236	4,970	15.6	95	25	Diabetes	CLD
8	M/45	RFMP	6c	789,285	71	117	7,400	15.2	110	Nil	-	-
9	M/36	RFMP	6c	28,844,529	55	85	5,900	15.0	201	Nil	-	-
10	M/48	RFMP	6c	356,089	87	47	3,900	16.4	33	10	Diabetes	LC
11	F/45	RFMP	6c	Positive	72	91	6,900	13.1	195	Nil	-	CLD
12	F/50	Direct sequencing	6c	10,266,000	25	33	6,000	13.2	247	Nil	-	-
13	F/40	RFMP	6c	1,260,000	157	189	6,000	14.9	186	Nil	-	CLD
14	M/40	RFMP	6	1,650,000	38	56	5,100	15.6	147	Nil	-	-
15	M/41	RFMP	6c	9,330,000	43	21	7,300	16.8	162	30	HBsAg+	-
16	F/39	RFMP	6a/c	1,127,568	127	46	4,360	12.3	132	Nil	-	-
17	F/36	RFMP	6c	13,068,693	50	71	4,790	13.8	174	60	-	-
18	M/43	RFMP	6c	1,260,000	157	189	5,500	14.9	186	Nil	Diabetes	-
19	F/43	RFMP	6/6c	4,980,000	96	140	5,700	15.7	238	Nil	HBsAg+	-
20	M/54	Direct sequencing	6c	131,000	183	373	4,200	13.7	176	Nil	-	-
21	M/47	RFMP	6c	9,040,000	34	63	5,800	14.3	279	Nil	-	-
22	F/56	RFMP	6c	1,390,000	88	136	5,300	13.1	165	Nil	-	-
23	F/57	RFMP	6c	459,000	45	29	3,600	13.2	155	Nil	-	-
24	M/44	RFMP	6c	2,720,000	102	190	5,200	15.1	177	20	-	-
25	M/49	RFMP	6c	975,000	100	64	4,700	15.2	54	Nil	-	LC
26	M/49	RFMP	6c	96,500	151	479	5,300	16.9	233	Nil	-	-
27	M/40	RFMP	6c	1,420,000	56	67	8,400	16.4	136	10	HBsAg+	-
28	M/50	RFMP	6c	637,000	82	173	5,800	15.7	122	Nil	-	-
29	M/34	RFMP	6c	1,270,000	139	350	4,900	16.9	243	20	-	-
30	F/38	RFMP	6c	7,000,000	54	33	5,500	13.5	191	Nil	-	-
31	M/37	RFMP	6c	609,300	1,123	1,019	4,560	16.1	103	40	-	-
32	F/39	RFMP	6c	9,106,107	24	24	5,640	13.1	178	Nil	-	-

HCV, hepatitis C virus; AST, aspartate transferase; ALT, alanine transferase; WBC, white blood cell; Hb, hemoglobin; US, ultrasonography; M, male; INNO-LiPA, line probe assay; RFMP, restriction fragment mass polymorphism; F, female; CLD, chronic liver disease; LC, liver cirrhosis; HBsAg+, hepatitis B surface antigen positive.
*Estimated amount.

two were relapsed and one attained SVR (p=0.301).

Most common adverse event was flu-like syndrome, and dose reduction was necessary in 24% (6/25) of patients. There was no treatment discontinuation by adverse events.

DISCUSSION

HCV genotype 6 is geographically restricted in South East Asia and surrounding regions, where 30% to 50% of all hepatitis C patients are infected with genotype 6.[9-11] Diverse subtypes of genotype 6 are accumulated and newly isolated subtypes are almost always reported in this area. So, it is suggested that genotype 6 may have been long circulated or evolved within Southeast Asia, and transmitted to the adjacent countries.[12] Whereas most data about genotype 6 HCV were centered on these regions, there have been not many data in Korea probably due to low prevalence of HCV genotype 6. While Shin *et al*.[13] recently reported the prevalence of genotype 6 as 10.5%, most

Table 2. Treatment Profile of Patients with Genotype 6 Who Received Peginterferon and Ribavirin

No.	PEG-IFN	Initial ribavirin dose, mg	PEG-IFN adherence, %	Ribavirin adherence, %	Intended treatment duration	RVR	EVR	ETR	SVR
1	2a	800	100	100	24	-	cEVR	Yes	Relapse
2	2a	600	100	100	24	No	No	-	Nonresponder
3	2a	1,000	100	100	48	-	pEVR	Yes	Relapse
4	2a	1,000	100	100	48	Yes	cEVR	Yes	Yes
5	2a	1,000	79	83	48	Yes	cEVR	Yes	Yes
6	2a	1,000	93	95	48	-	pEVR	Yes	Yes
8	2a	900	100	100	24	-	cEVR	Yes	Yes
9	2b	1,200	100	100	48	No	No	No	Nonresponder
10	2b	800	100	100	24	-	cEVR	Yes	Relapse
11	2b	1,000	100	100	24	-	cEVR	Yes	Relapse
12	2a	1,000	100	100	24	No	pEVR	Yes	Relapse
13	2a	1,000	100	100	16	-	cEVR	-	F/U loss
14	2a	1,000	100	100	13	-	cEVR	-	F/U loss
15	2b	1,000	100	100	48	No	cEVR	Yes	Yes
16	2b	1,000	84	82	54	Yes	cEVR	Yes	Yes
17	2a	800	98	100	48	No	cEVR	Yes	Yes
18	2a	1,000	100	82	48	-	cEVR	Yes	Yes
19	2a	1,000	100	100	48	-	cEVR	Yes	Yes
20	2a	1,000	100	100	24	Yes	cEVR	Yes	Yes
21	2b	800	100	100	24	No	cEVR	Yes	Yes
22	2b	800	100	100	48	-	cEVR	Yes	Relapse
23	2b	800	100	75	24	Yes	cEVR	Yes	Relapse
28	2b	1,000	100	100	24	No	cEVR	Yes	Yes
29	2b	1,000	100	100	48	Yes	cEVR	Yes	Yes
32	2b	800	100	100	20	No	cEVR	-	F/U loss

PEG-IFN, peginterferon; RVR, rapid virologic response; EVR, early virologic response; ETR, end of treatment response; SVR, sustained virologic response; cEVR, complete early virologic response; pEVR, partial early virologic response; F/U, follow up.

other studies reported the prevalence as about 1.0%.[8,13-15] The affiliated hospital of Shin *et al*.[13] is located where many immigrants from Southeast Asia and China and drug abusers exist, which may explain the higher prevalence than others.

Genotype 6 HCV is highly diverse with 23 subtypes and certain subtypes have different geographic predominance like genotypes; 6a in South China, Taiwan, and Hong Kong, 6n in Myanmar, 6f in Thailand, and 6g in Indodesia.[1,16] Until recently, subtype 6c is an overwhelming subtype regardless of genotyping methods in Korea.[13-15] Interestingly, clustered 6c has not been reported but in Korea since first isolated as a sole strain from a commercial blood donor in Thailand.[17] We assume that 6c is a rare HCV variant and its spread within Korea might be related with migration of some hosts.

In this study, RFMP was most commonly used, that is known as accurate for HCV genotyping. On the other hand, INNO-LiPA HCV II (Innogenetics) has been criticized due to less complete ability to distinguish genotype 6 from 1, especially 6a from 1b.[15,18-21] Although a gold standard for genotyping and subtyping is direct sequencing assay, RFMP assay could distinguish mass differences between oligonucleotide fragment levels and be most reliable modality among commercial kits. We also suggest that further study is required to investigate the prevalence and distribution of each subtypes of genotype 6 with direct sequencing or combining two or more modalities.

To date, virological and clinical features of hepatitis C genotype 6 are known to be not significantly different to genotype 1, and 2/3.[1,16,22] However, Korean patients infected with genotype 6 tend to be younger and have chronic hepatitis rather than advanced stage such as hepatocellular carcinoma or cirrhosis.[11,23] These suggest that it has been not so long since a transmission into Korea and propagation of HCV genotype 6 occurred. We would prevent further amplification of genotype 6 infection in Korea by tracking human migration and transmission route of genotype 6 HCV.

Genotype is an important factor of response to treatment.

Prior studies have suggested that the HCV genotype 6 has responded to the IFN-based treatment better than genotype 1 but less than genotype 2/3. The 48-week treatment may be more effective to achieve SVR than 24-week treatment in PEG-IFN and ribavirin combination. Those who achieve RVR may receive the shorter 24-week treatment.[23-27] Despite statistically insignificant with too small sample size, our results showed a similar trend to the prior data. In our study, SVR rates were 40% and 75% according to the 24- and more than 48-week of PEG-IFN and ribavirin treatment respectively and RVR showed high positive predictive value (83%).

Since the introduction of DAA, a treatment paradigm for CHC has been rapidly changing. Combination of PEG-IFN and ribavirin is not recommended as a standard treatment of genotype 1 anymore and plays a minimal role even in genotype 2/3.[5,28,29] However, unlike the major genotypes of HCV infection, data about minor genotypes such as genotype 6 are still limited.[6,30] In addition, a surpassing cost per SVR of DAA is a major hurdle in the real world.[31,32] Considering that a compulsory public health care system exists in Korea, where the lowest cost per cure is a more valuable, PEG-IFN and ribavirin could not be discarded yet. Therefore, we consider the results of our study are still meaningful for guide to treat patients infected with genotype 6 HCV.

This is a retrospective study. Nevertheless, a prospective study about genotype 6 HCV is hardly to be established due to low prevalence. To overcome inhomogeneity of enrolled patients and treatment regimen, the subjects were limited as Koreans.

In this study, we showed that Korean patients infected genotype 6 HCV tended to be younger and have relatively short infection duration comparing to those who in the prevalent area. In Korea, 6c is the most common subtype. When treated with PEG-IFN and ribavirin combination, the overall SVR rate was observed as 52% (13/25) in patients. As like other HCV infection, longer duration of treatment and attainment of RVR are favorable to achieve SVR in genotype 6 HCV infection. Although the treatment profile of our study is not an updated one, we believe that this is valuable data to have insights regarding the evolution and spread of genotype 6 HCV in Korea and manage patients infected with genotype 6 HCV.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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