Body Mass Index and Nonresponse to Antiviral Treatment in Korean Patients with Genotype 2 and 3 Chronic Hepatitis C

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Pegylated-interferon plus ribavirin is the standard treatment for chronic hepatitis C. Sustained virological response (SVR) rates of up to 80% are reported in genotype 2 and 3 chronic hepatitis C cases. Obesity, a modifiable risk factor, may have a deleterious effect on antiviral treatment. We performed this study to examine the efficacy and safety of pegylated-interferon and ribavirin therapy in Korean patients with genotype 2 and 3 chronic hepatitis C and to investigate the risk factors for nonresponse to antiviral treatment. A total of 121 patients were treated with peginterferon alpha-2a 180 mcg/week plus ribavirin 800 mg/day for 24 weeks. The end-of-treatment virologic response (ETVR), the SVR, the end-of-treatment biochemical response (ETBR), the sustained biochemical response (SBR), and the adverse events were analyzed. The ETVR and SVR were 94.1% and 89.1%, respectively. The ETBR was 80.2% and the SBR was 96%. Multivariate analysis showed that a body mass index of 25 and over was the only independent factor that affected the SVR (odds ratio=10.5, 95% confidence interval: 2.006-54.948, p=0.005). Twenty patients (16.5%) dropped out at the end of treatment, and 7 (5.8%) patients discontinued treatment because of treatment-related adverse events. Our study showed that combination therapy with pegylated-interferon and ribavirin as an initial treatment for genotype 2 and 3 chronic hepatitis C is very effective and safe, and that body mass index is an independent risk factor for nonresponse to antiviral treatment in patients with genotype 2 and 3 chronic hepatitis C.

Key Words: *Hepatitis C, chronic; Peginterferon alfa-2a; Ribavirin; Body mass Index*

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INTRODUCTION

Hepatitis C virus (HCV) infection causes chronic liver disease and cirrhosis in a proportion of individuals, and its complications may develop relatively rapidly.[1] The World Health Organization estimates that approximately 170 million persons (3% of the world's population) are chronically infected with HCV, with 3 to 4 million new infections occurring each year.[2,3]

In Korea, the prevalence of HCV infection was 1.4% according to one study,[4] and genotype 1b and 2a were the most prevalent in anti-HCV (+) adults.[5] The current standard of care in the treatment of chronic hepatitis C (CHC) is combination therapy with pegylated-interferon (PEG-IFN) and ribavirin (RBV).

Interferons are naturally occurring proteins that promote the host immune response to viruses and that also act directly to inhibit viral growth or replication. Pegylated-interferons are produced by binding of the inert polyethylene glycol moiety to interferon molecules, thus decreasing renal clearance, altering metabolism, and increasing the half-life of the PEG-IFN molecule. RBV is a ribonucleoside analogue that has a broad spectrum of antiviral activity; it may act by enhancing the number of point mutations in the viral genome rather than by chain termination of replicating RNA. This mechanism has not yet been proven for HCV, and RBV alone is ineffective in treating chronic HCV infection. Recently, the combination of PEG-IFN and RBV has improved long-term response rates by decreasing the relapse rate.[6,7]

The HCV genotype has an important role in the response to antiviral treatment. Standard-of-care regimens achieve sustained virological response (SVR) rates of up to 80% in patients with genotype 2 and 3 CHC. This is compared with SVR rates of 40% to 50% in genotype 1 CHC.[8,9] In addition, the treatment duration varies depending on the HCV genotype. For patients infected with genotype 1 CHC, the recommended treatment duration is 48 weeks, whereas for patients infected with genotype 2 and 3 CHC, the recommended treatment duration is 24 weeks.[7,10] Considering this, genotype 2 and 3 CHC patients will be involved more positively in the course of treatment.

Obesity is often accompanied by hepatic steatosis or steatohepatitis that may augment fibrosis progression in persons with chronic HCV and adversely affect response to antiviral therapy.[11] Of those various risk factors for non-response to antiviral treatment, obesity may be the most significant modifiable factor.

Therefore, we performed this study to examine the efficacy and safety of PEG-IFN and RBV therapy in Korean patients with genotype 2 and 3 CHC and to investigate risk factors including obesity for nonresponse to antiviral treatment.

MATERIALS AND METHODS

1. Patients

In this retrospective study, a total of 121 patients with chronic HCV genotype 2 or 3 infection who were treated with PEG-IFN and RBV therapy between July 2004 and September 2010 at Chonnam University Medical School Hospital were enrolled. Eligible subjects included adult patients who had never received antiviral treatment, including interferon treatment, and who tested positive for both anti-HCV antibody and serum HCV RNA for over 6 months. All patients gave written informed consent.

Patients were excluded from the study if they had HCV genotype infection other than type 2 or 3, hemoglobin concentration <10 g/dl, neutrophil count $<750/mm^3$, platelet count $<50\times10^3/mm^3$, serum creatinine >1.4 mg/dl, evidence of advanced liver disease, uncontrolled hypertension or heart failure, severe coronary artery disease, uncontrolled diabetes mellitus or obstructive pulmonary disease, current alcohol misuse or history of alcohol misuse (>20 g/day), psychiatric condition, autoimmune hepatitis, previous liver transplantation, evidence of hepatocellular carcinoma, abnormal thyroid function, pregnancy or inability to achieve proper contraception, or drug hypersensitivity.

2. Determination of HCV infection and HCV subtypes

Positivity for anti-HCV antibody was demonstrated by CMIA (chemi-luminescent-microparticle-immunoassay). Serum HCV RNA was detected by RT-nested PCR (reverse transcriptase-nested polymerase chain reaction), and serum HCV load was quantitatively determined by real-time PCR (ABI 7,300 real time system®, USA). HCV RNA genotype was determined by RFMP (restriction fragment mass polymorphism).

3. Study design

Enrolled patients were treated with weekly injections of PEG-IFN alpha-2a (Pegasys®; F. Hoffmann-La Roche Ltd., Basel, Switzerland) at 180 mcg plus oral administration of RBV at 800 mg for 24 weeks.

Patients visited the clinic every 1 to 4 weeks until week 24 and then for an additional follow-up visit 24 weeks after completing treatment. HCV RNA was measured at baseline, week 12, the end of treatment, and at 24 weeks after treatment completion. Laboratory measurements included hemoglobin, neutrophil counts, platelet counts, and liver function tests every 1 to 4 weeks and thyroid function tests at baseline and at the end of treatment. Adverse events were monitored and handled according to the manufacturers' instructions for the different tests.

4. Dose modifications

The dose of PEG was decreased or discontinued according to the degree of neutropenia, thrombocytopenia, or elevated serum alanine aminotransferase (ALT). When laboratory results showed neutrophil counts $<750/mm^3$, the dose of PEG was decreased by 75% and when neutrophil counts were $<500/mm^3$, PEG injection was discontinued. When neutrophil counts were recovered at $\geq1,000/mm^3$, a 50% decreased dose of PEG was restarted and neutrophil counts were monitored intensively. When platelet counts were $50,000/mm^3$ to approximately $30,000/mm^3$, the dose of PEG was decreased by 50%. When platelet counts were $<30,000/mm^3$, PEG injection was discontinued. Full doses were resumed when the event was resolved.

When serum ALT elevation continued abnormally, the dose of PEG was decreased by 50%. When serum ALT elevation continued despite a dose decrease, serum bilirubin increased, or hepatic failure developed, the PEG injection was discontinued.

When the hemoglobin concentration decreased to <10 g/dl, the dose of RBV was lowered to 600 mg/day, and when the hemoglobin concentration decreased to <8 g/dl, the administration of RBV was discontinued. In the case of interruption of RBV administration, PEG monotherapy was recommended for the rest of the treatment duration. When anemia was resolved, RBV administration was restarted.

5. Assessment of efficacy

The primary study endpoint was the SVR, which was defined as PCR-negative serum HCV RNA by the end of treatment and 24 weeks after treatment completion. Early virologic response (EVR) was defined as at least a 2-log drop in HCV RNA compared with baseline or an unquantifiable or undetectable test result at study week 12. End-of-treatment virological response (ETVR) was defined as PCR-negative serum HCV RNA at the end of treatment. The secondary treatment response point was to assess the sustained biochemical response (SBR), which was defined as normalization of serum ALT 24 weeks after treatment completion.

The end-of-treatment biochemical response (ETBR) was defined as normalization of serum ALT at the end of treatment.

6. Statistical analysis

Statistical analyses were performed by using the SPSS V.17.0 statistical package (SPSS Inc, Chicago, IL, USA). Group means composed of continuous data were analyzed by using the paired-sample t-test and are presented as mean values with standard deviations (SDs). Categorical variables were analyzed with the Pearson chi-squared test or the Fisher exact test as appropriate. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were also calculated. All p values < 0.05 by two-tailed tests were considered significant. Multivariate logistic regression analysis was used to establish the factors contributing to efficacy and discontinuation of therapy.

RESULTS

1. Baseline patient characteristics

All 121 patients enrolled in the study were included in the final analysis. The distribution of subtypes of genotype 2 or 3 CHC among the patients was as follows: 85 (70.2%) patients had subtype 2a/c, 28 (23.1%) patients had single type 2, 4 (3.3%) patients had subtype 2a, 3 (2.5%) patients had subtype 2b, and a single (0.8%) patient had subtype 3a. The clinical and laboratory characteristics of the patients at baseline are shown in Table 1. Of the 121 patients who received treatment, 105 (86.8%) completed the 24 weeks of treatment and 101 (83.5%) completed both treatment and the post-treatment follow-up period (Fig. 1). A total of 7 (M:F= 2:5) patients discontinued treatment because of adverse events and 13 (M:F=9:4) patients did not follow-up until 24 weeks after completing treatment.

TABLE 1. Baseline characteristics of the patients

Characteristic	Value
Number of patients	121
Age (years, mean±SD)	49.7±11.4
20-29 years (n; %)	8 (6.6%)
30-39 years (n; %)	12 (9.9%)
40-49 years (n; %)	35 (28.9%)
50-59 years (n; %)	41 (33.9%)
60-69 years (n; %)	25 (20.7%)
Sex (male/female)	72/49
Body mass index (kg/m^2, mean±SD)	23.9±3.0
HCV RNA (×10^6 IU/ml, mean±SD)	1.9±5.0
Diabetes mellitus (%)	13 (10.7%)
Hypertension (%)	16 (13.2%)
AST (U/L)	92.9±106.8
ALT (U/L)	125.5±204.5
ALP (U/L)	91.7±34.8
T-bilirubin (mg/dl)	0.9±0.5
Albumin (g/dl)	4.4±0.7

AST: aspartate aminotransferase, ALT: aspartate aminotransferase; ALP: alkaline phosphatase.

2. Virological response

At treatment week 12, EVR was attained by 96.5% of patients and at the end of treatment, 97.1% of patients attained ETVR. Additionally, 89.1% of patients attained SVR at 24 weeks after treatment completion. ETBR was 80.6% and SBR was 96.0% (Fig. 2). Two (2.0%) nonresponder patients remained viremic throughout therapy. These were obese patients with a body mass index of 25.71 and 26.06 (kg/m^2), respectively.

3. Univariate and multivariate logistic regression analyses of the factors associated with treatment response

Univariate and multivariate logistic regression analyses were performed to evaluate the various factors influencing efficacy of PEG plus RBV therapy. As indicated in Table 2, univariate analysis showed that body mass index of 25 (kg/m^2) was an important factor for the achievement of SVR by PEG plus RBV therapy (p=0.005). Patient age, HCV RNA level, and drug dose reduction were not significant influences on the achievement of SVR (p > 0.5). The multivariate analysis revealed a BMI of 25 (kg/m^2) to be independently associated with SVR (Table 3).

4. Side effects and tolerability

Until treatment week 12, three patients discontinued therapy because of adverse events (neutropenia in two patients and flu-like symptoms in one patient). Additionally, until the end of treatment, four patients discontinued therapy because of hyperthyroidism, neutropenia, flu-like
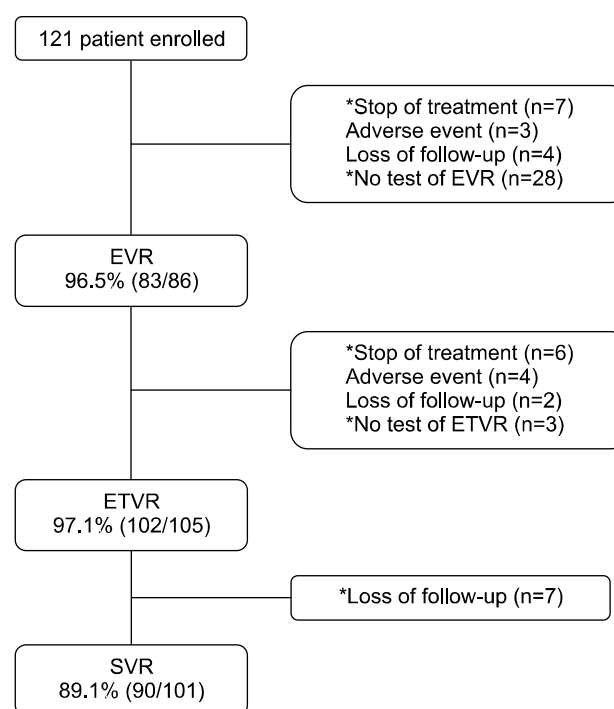

FIG. 1. Patient flow diagram. EVR: early virologic response, ETVR: end-of-treatment virologic response, SVR: sustained virologic response, n: number.
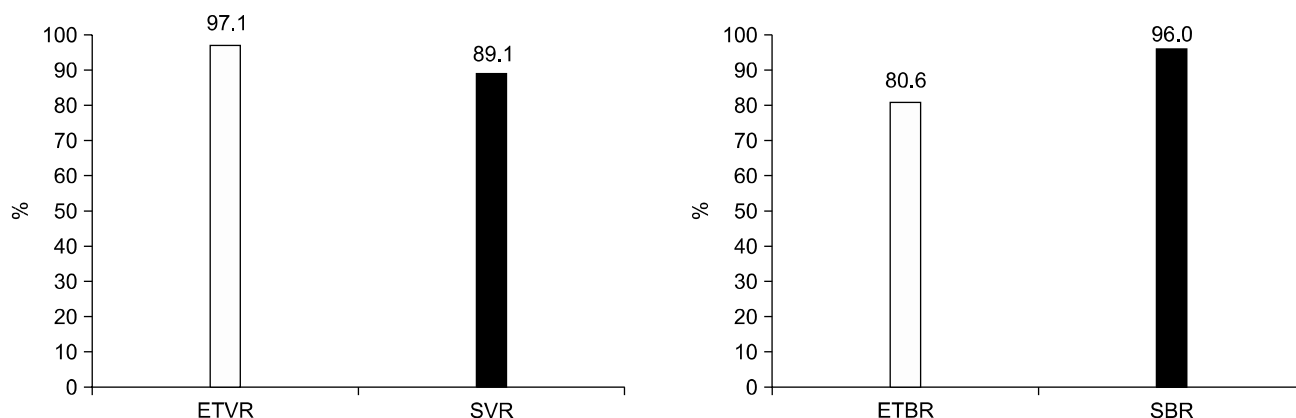
FIG. 2. Treatment response. End-of-treatment virologic response (ETVR) was 97.1% and sustained virologic response (SVR) was 89.1%. End-of-treatment biochemical response (ETBR) was 80.6% and sustained biochemical response (SBR) was 96.0%.

TABLE 2. Univariate analysis: factors influencing the sustained virologic response

	Patients with SVR (n=90)	Patients without SVR (n=11)	p value
Age (years, mean±SD)	48.8±11.6	50.7±7.8	0.484[*]
<60 years (n; %)	74 (82.2%)	10 (90.9%)	0.685
≥60 years (n; %)	16 (17.8%)	1 (9.1%)	
Sex (male/female)	54/36	7/4	1.0
HCV RNA (×10^6 IU/ml, mean±SD)	1.8±4.1	1.6±2.6	0.887[*]
Diabetes mellitus (%)	12 (14.1%)	0 (0.0%)	0.590[†]
Hypertension (%)	14(16.5%)	1 (12.5%)	1.0
AST (U/L)	85.7±91.5	71.4±36.9	0.338
ALT (U/L)	118.1±185.6	81.2±54.4	0.155
ALP (U/L)	89±33.2	79.7±23.2	0.255
T-bilirubin (mg/dl)	0.8±0.3	0.8±0.4	0.91
Albumin (g/dl)	4.4±0.7	4.4±0.4	0.975
BMI (kg/m^2)			
Mean	23.42±3.04	25.48±2.68	0.056[*]
<25	58 (72.5%)	2 (22.2%)	0.005[†]
≥25	22 (27.5%)	7 (77.8%)	
PEG-IFN total dose			0.575[†]
100%	46 (51.1%)	4 (36.4%)	
>75%	40 (44.4%)	7 (63.6%)	
50-75%	4 (4.4%)	0 (0.0%)	
Ribavirin total dose			0.638[†]
100%	52 (57.8%)	5 (45.5%)	
>80%	28 (31.1%)	5 (45.5%)	
<80%	10 (11.1%)	1 (9.1%)	

[*]Paired sample t-test, [†]Fisher's exact test. SVR: sustained virologic response, BMI: body mass index, PEG-IFN: pegylated interferon, n: number, AST: aspartate aminotransferase; ALT: aspartate aminotransferase, ALP: alkaline phosphatase.

symptoms, and tingling sensation for each of the four patients, respectively. However, no serious adverse events were reported. The most commonly reported adverse events of special interest were hematological disorders [anemia: 43 (35.5%), neutropenia: 77 (63.6%), and thrombocytopenia: 46 (38%)], and most of them were controlled well by drug dose reduction. Six patients had thyroid function abnormalities (hypothyroidism and hyperthyroidism in three patients each). Other adverse events were typically those previously reported for PEG plus RBV therapy [flu-like symptoms: 41 (33.9%), fatigue: 28 (23.1%), itching sense: 23 (19.0%), anorexia: 20 (16.5%), headache: 17 (14.0%), epigastric discomfort: 15 (12.4%), rash: 13 (10.7%), hair loss: 12 (9.9%), dry cough: 9 (7.4%), dizziness: 9 (7.4%), insomnia: 5 (4.1%), dyspnea: 4 (3.3%), and depression: 2 (2.0%)].

DISCUSSION

Within our single clinic, we showed that the SVR in the treatment for genotype 2 and 3 CHC was 89.1%. In large-scale studies in the West, the SVR in the treatment

TABLE 3. Multivariate analysis: factors influencing the sustained virologic response

	OR	95% C.I	p value*
Age < 60 years	0.516	0.049-5.461	0.690
HCV RNA < 0.6×10^6 IU/ml	0.580	0.117-2.887	0.571
BMI < 25 kg/m^2	10.5	2.006-54.948	0.005
PEG-IFN total dose	1.222	0.322-4.641	0.707
Ribavirin total dose	1.515	0.521-4.404	0.441

*p value was obtained by multivariate logistic analysis. BMI: body mass index, PEG-IFN: pegylated interferon.

of genotype 2 and 3 CHC has been reported to be between 76% and 82%.[8,9] According to previous reports in Korea, the SVR in the treatment of genotype 2 and 3 CHC was between 67.3% and 94.1%.[12-14] Thus, compared with extensive clinical studies in the West and other domestic studies, the SVR we report here is higher.

Differences in characteristics between racial groups, which potentially confound the contribution of race/ethnicity to the observed response to antiviral therapy, need to be considered. As anticipated, Asians (non-South Asians) have a lower body weight and thus received the highest dose of RBV per kilogram body weight.[15,16] Low body weight and body mass index (BMI) are potential factors that confound the observed high rates of SVR in Asians (non-South Asians).

Previous studies revealed that host factors associated with reduced rates of SVR include obesity, insulin resistance (and overt diabetes), presence of advanced fibrosis or hepatic steatosis, and both patterns of hepatic gene expression and polymorphisms of the interferon-λ gene.[17,18] In patients with chronic hepatitis C, the degree of hepatic steatosis and fibrosis has been shown to correlate with BMI, and steatosis may be an important cofactor in both accelerating fibrosis and increasing liver necroinflammatory activity in chronic hepatitis C.[19,20]

Among these factors, obesity may be regarded as a modifiable risk factor.[11,21] Previous studies have used weight as a marker to define obesity. However, a more accurate way to separate individuals according to their body habitus may be by a measure indirect of total body fat content. The BMI, which describes relative weight for height, correlates with total body fat content,[22] whereas weight on its own may not.

Bressler et al reported that obesity (BMI ≥ 30 kg/m^2) is a negative predictor of SVR when weight-based dosing of RBV was not used.[23] In the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) study for weight-related effects on disease progression, the median BMI of enrolled patients was 29.2 kg/m^2.[24] But there have been no specific previous studies about the relationship between BMI and SVR in Korea. BMI ≥ 25 kg/m^2 was a negative predictor of SVR in our study and this result should be considered as a difference between the East and

the West.

Unfortunately, at our clinic, liver biopsy was not done in patients with genotype 2 and 3 CHC and thus we could not show an association between the presence of steatosis and obesity. One study reported that HCV genotype 3a was associated with steatosis independent of body weight,[25] and the response of patients with genotype 3a to antiviral treatment indicated that it could not be hepatic steatosis alone that decreases the antiviral response.

Among our enrolled patients, genotype 3a was observed in only one patient who was obese (BMI=26.2 kg/m^2). However, he missed the follow-up after treatment completion. To evaluate the association between steatosis and BMI, further studies will be needed.

Obesity is also associated with the absorption of PEG-IFNs. The structural property of some PEG-IFNs is such that their size precludes rapid uptake into the vascular system. Large proteins (> 15 kD) injected subcutaneously are primarily taken up by the lymphatic system.[26] Standard IFN is absorbed through blood capillaries and the lymphatic circulation. However, because of the size of some PEG-IFNs, they may be predominantly taken up by the lymphatics. Obese people are known to have poor lymphatic circulation,[27] and this could lead to lower serum levels of PEG-IFN, thus diminishing the likelihood of a successful antiviral response.

In our study, patient age, HCV RNA level, and drug dose reduction did not significantly influence the achievement of SVR (p > 0.5). An uneven baseline age distribution of the patients, low body weight compared with the West, and race-specific host genetic variation could have affected these results.

Genetic polymorphisms of human leukocyte antigen, TNFa-308 promoter gene, suppressor of cytokine signaling (SOCS)-3 gene, and interferon-k 28B (IL28B) are examples of host-related differences that may influence the response to interferon.[17,28,29]

Adherence to therapy is a key factor in achieving an SVR. In this study, 86% patients experienced constitutional symptoms and 94.2% of patients experienced all adverse effects including hematologic events. Similar adverse effects due to PEG plus RBV therapy have been described in almost every organ system.[30] PEG and RBV side effects may differ between races, but Asians compared with Westerners seem to have more side effects because they have lower body weight and do not control the dose of drug. In this study, neutropenia, thrombocytopenia, and anemia developed in 63.6%, 38%, and 35.5% of patients, respectively. However, dose reduction of the PEG-IFN and RBV was done for 45.5% and 24.8% of patients, respectively.

Hyperthyroidism and hypothyroidism developed in 6 (3:3) patients, and one patient with hyperthyroidism stopped PEG plus RBV therapy 24 weeks after the treatment started. In this study, although many side effects developed, the treatment withdrawal rate due to adverse events was 5.8%, and no serious adverse events were reported. Instead, 10.7% of patients were lost in follow-up. Suppor-

tive strategies to improve adherence will increase overall SVR rates.

In conclusion, the results of this study show that combination therapy with PEG-IFN and RBV as an initial treatment for genotype type 2 and 3 CHC is very effective and safe. Our results show that BMI should be regarded as a significant factor influencing the SVR following a course of antiviral treatment.

REFERENCES

1. Di Bisceglie AM. Natural history of hepatitis C: its impact on clinical management. Hepatology 2000;31:1014-8.
2. Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med 2001;345:41-52.
3. WHO. Hepatitis C: global prevalence (update).
4. Kim YS, Pai CH, Chi HS, Kim DW, Min YI, Ahn YO. Prevalence of hepatitis C virus antibody among Korean adults. Korean Med Sci 1992;7:333-6.
5. Lee YS, Chung YH, Min YI, Moon DH, Na DS, Suh DJ. Hepatitis C virus genotyping of 100 consecutive anti-HCV positive cases with PCR using type=specific primers. Korean J Hepatol 1998;4:235-43.
6. Sievert W. Management issues in chronic viral hepatitis: hepatitis C. J Gastroenterol Hepatol 2002;17:415-22.
7. Strader DB, Wright T, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C. Hepatology 2004;39:1147-71.
8. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001;358:958-65.
9. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçales FL Jr, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347:975-82.
10. NIH Consensus Statement on Management of Hepatitis C: 2002. NIH Consens State Sci Statements 2002;19:1-46.
11. Charlton MR, Pockros PJ, Harrison SA. Impact of obesity on treatment of chronic hepatitis C. Hepatology 2006;43:1177-86.
12. Lee H, Choi MS, Paik SW, Kim JH, Kim DY, Lee JH, et al. Peginterferon alfa-2a plus ribavirin for initial treatment of chronic hepatitis C in Korea. Korean J Hepatol 2006;12:31-40.
13. Hwang SY, Lee HJ, Park KT, Kim KY, Lee SM, Park CW, et al. Effectiveness and complications of combination therapy with interferon alpha and ribavirin in patients with chronic hepatitis C. Korean J Gastroenterol 2007;49:166-72.
14. Lee HJ, Eun JR, Choi JW, Kim KO, Moon HJ. Comparison of therapeutic results between combination therapy of peginterferon alpha-2a plus ribavirin and interferon alpha-2b plus ribavirin according to treatment duration in patients with chronic hepatitis C. Korean J Hepatol 2008;14:46-57.
15. Missiha S, Heathcote J, Arenovich T, Khan K; Canadian Pegasys Expanded Access Group. Impact of asian race on response to combination therapy with peginterferon alfa-2a and ribavirin in chronic hepatitis C. Am J Gastroenterol 2007;102:2181-8.
16. Pattullo V, Heathcote EJ, Wong DK. Superior response to pegylated interferon and ribavirin in Asians with chronic hepatitis C. Hepatol Int 2010;4:723-31.
17. Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature 2009;461:399-401.
18. Tanaka Y, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Sakamoto N, et al. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. Nat Genet 2009;41:1105-9.
19. Hourigan LF, Macdonald GA, Purdie D, Whitehall VH, Shorthouse C, Clouston A, et al. Fibrosis in chronic hepatitis C correlates significantly with body mass index and steatosis. Hepatology 1999;29:1215-9.
20. Clouston AD, Jonsson JR, Purdie DM, Macdonald GA, Pandeya N, Shorthouse C, et al. Steatosis and chronic hepatitis C: analysis of fibrosis and stellate cell activation. J Hepatol 2001;34:314-20.
21. Zeuzem S, Feinman SV, Rasenack J, Heathcote EJ, Lai MY, Gane E, et al. Peginterferon alfa-2a in patients with chronic hepatitis C. N Engl J Med 2000;343:1666-72.
22. Wellens RI, Roche AF, Khamis HJ, Jackson AS, Pollock ML, Siervogel RM. Relationships between the Body Mass Index and body composition. Obes Res 1996;4:35-44.
23. Bressler BL, Guindi M, Tomlinson G, Heathcote J. High body mass index is an independent risk factor for nonresponse to antiviral treatment in chronic hepatitis C. Hepatology 2003;38:639-44.
24. Everhart JE, Lok AS, Kim HY, Morgan TR, Lindsay KL, Chung RT, et al. Weight-related effects on disease progression in the hepatitis C antiviral long-term treatment against cirrhosis trial. Gastroenterology 2009;137:549-57.
25. Adinolfi LE, Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. Hepatology 2001;33:1358-64.
26. Porter CJ, Charman SA. Lymphatic transport of proteins after subcutaneous administration. J Pharm Sci 2000;89:297-310.
27. Banerjee D, Williams EV, Ilott J, Monypenny IJ, Webster DJ. Obesity predisposes to increased drainage following axillary node clearance: a prospective audit. Ann R Coll Surg Engl 2001;83:268-71.
28. Yu ML, Dai CY, Chen SC, Chiu CC, Lee LP, Lin ZY, et al. Human leukocyte antigen class I and II alleles and response to interferon-alpha treatment, in Taiwanese patients with chronic hepatitis C virus infection. J Infect Dis 2003;188:62-5.
29. Persico M, Capasso M, Russo R, Persico E, Crocè L, Tiribelli C, et al. Elevated expression and polymorphisms of SOCS3 influence patient response to antiviral therapy in chronic hepatitis C. Gut 2008;57:507-15.
30. Russo MW, Fried MW. Side effects of therapy for chronic hepatitis C. Gastroenterology 2003;124:1711-9.