

Review

KASL clinical practice guidelines: Management of Hepatitis C

The Korean Association for the Study of the Liver (KASL)*

PREAMBLE

Aims

Practice Guidelines for Management of Hepatitis C were first established in 2004. Since then, many study results have been published concerned with epidemiology, clinical outcomes and related factors, concept of response-guided therapy, therapeutic strategy, and results. Moreover, as direct acting antivirals (DAA) have been recently developed and adapted to practice, treatment of hepatitis C is rapidly evolving. Therefore, the Korean Association for the Study of the Liver (KASL) revised the guidelines based on a systematic approach that reflects evidence-based medicine and expert opinions.

The clinical practice guidelines for the management of hepatitis C have been revised to be useful for treatment, research, and education. These recommendations are not absolute standards of care, and adoption of the guidelines in clinical practice may differ for individual patients.

Target population

The target groups of these guidelines are newly or previously

diagnosed patients with hepatitis C virus (HCV) infection, including not only chronic hepatitis C and cirrhosis, but also acute hepatitis C patients, hepatitis C patients under special medical conditions, such as intravenous drug use (IVDU), those with chronic kidney diseases, coinfection of human immunodeficiency virus (HIV) or hepatitis B virus (HBV), and pediatric patients.

Intended users

The guidelines are intended to provide useful information and guidance to physicians and healthcare providers involving in the diagnosis and treatment of hepatitis C, and resident physicians, practitioners, and trainers.

Development, funding, and revision

The Clinical Practice Guidelines Committee for the Management of Hepatitis C (Committee) consisting of nine hepatologists was organized according to the proposal and with approval of the KASL Board of Executives. Funding for the revision was provided by KASL. Each committee member collected and analyzed the source data in his/her own field of expertise. The members then wrote the manuscript together.

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Literature review for evidence collection

The committee systematically collected and reviewed the international and domestic literature published in Pubmed, MEDLINE, KoreaMed, and other databases. The key words used were 'hepatitis C virus', 'hepatitis C', 'liver cirrhosis', 'liver cancer', and other related specific key words.

Levels of evidence and grades of recommendations

The quality of evidence was classified according to the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system (Table 1).¹ Based on the types of studies, randomized, control studies were approached from a high level of evidence, while observational studies were approached from a low level of evidence. The level of evidence was adjusted by accounting for the factors influencing the quality of the studies. Through follow-up studies, the level of evidence was defined as follows: A, indicating the highest level of evidence with the smallest possibility of any changes in the conclusion; B, indicating a moderate level of potential changes; and C, indicating the lowest level of evidence with the greatest possibility of any changes.

The strength of a recommendation was also classified according to the GRADE system. Each study was classified as strong recommendation (1) or weak recommendation (2) under overall consideration of quality of evidence, the balance between the desirable and undesirable effect of an intervention, and socioeconomic aspects including cost or availability. A strong recommendation indicated that the interventions could be applied in most patients

with high degree of certainty and that there was a greater possibility of desirable effects, high-quality evidence, and presumed patient-important outcomes, cost-effectiveness, preference, and compliance. A weak recommendation indicated a suggestion made with less certainty but that could be considered favorable for many patients, based on the level of evidence, cost, or preferences of the patients or medical practitioners.

List of key questions

The revision committee considered the following clinical questions as the key components to be covered in these guidelines.

1. What is the epidemiology and natural history of hepatitis C in South Korea?
2. How should the diagnosis and evaluation of severity of chronic hepatitis C be made?
3. What is the goal of treatment and who are the targets for the antiviral treatment of hepatitis C?
4. How is the treatment response defined, and what are predictors of the response?
5. How are patients with chronic HCV genotype 1 and 4 infections treated?
6. How are patients with chronic HCV genotype type 2, 3, and 6 infections treated?
7. How are patients with acute hepatitis C treated?
8. How are the adverse effects of antiviral drugs managed and how the patients monitored during and after antiviral treatment?
9. How are patients with special conditions (cirrhosis, liver

Table 1. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE)

Criteria	
Quality of evidence	
High (A)	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate (B)	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low (C)	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any change of estimate is uncertain.
Strength of recommendation	
Strong (1)	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost.
Weak (2)	Variability in preference and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption.

Of the quality levels of evidence, we excluded "very low quality (D)" in our guideline for convenience, which was originally included in the GRADE system.

transplant and other organ transplants, immunosuppressive therapy or cytotoxic chemotherapy, intravenous drug use, chronic kidney diseases, coinfection with HIV or HBV, hemophilia, and pediatric patients) treated?

Review of the manuscript and approval process

Each version of the manuscript written by committee members was reviewed, agreed, and approved through meetings of the committee. The quality of the manuscript was evaluated based on the standards suggested by AGREE II (Appraisal of Guidelines for Research and Evaluation II) along with the academic integrity of the contents. The guidelines were reviewed after counsel from three specialists, one in each division including infectious diseases, renal diseases, and pediatrics. The guidelines were reviewed at a meeting of an external review board composed of 14 KASL members, and were further modified following opinions collected at a public hearing, and a symposium open to all KASL members. The final manuscript was approved by the KASL Board of Executives.

Release of the guidelines and plan for updates

The Korean version of the KASL Clinical Practice Guidelines for the Management of Hepatitis C was released and published in December 2013 on the KASL web site (<http://www.kasl.org>). Future revisions will be conducted under the judgment that the revision is necessary for the promotion of health in South Korea as further research data on the management of hepatitis C accumulates. In addition, use of DAA is to be allowed in South Korea in the near future, so that updates or partial revision of the guidelines will be warranted as appropriate.

EPIDEMIOLOGY

HCV is one of the main causes of acute and chronic hepatitis, cirrhosis, and hepatocellular carcinoma.² Hepatitis C is on the National Notifiable Infectious Disease list in South Korea and has been under surveillance since 2000. An effective HCV vaccine is yet to be discovered, so that understanding of national epidemiology and preventive strategies to block routes of HCV infection is important for public health.

Prevalence rate of HCV infection

Worldwide prevalence of HCV infection was 2.8% in 2005, equating about 185 million persons positive for antibody to hepatitis C (anti-HCV).^{3,4} The prevalence rate varies in different global regions; regions with high prevalence rate of over 3.5% include Central Asia covering Mongolia, China, South-East Asia covering Pakistan and Thailand, and North Africa covering Egypt. Low prevalence (below 1.5%) regions are Asia including South Korea and Japan, North America including the United States (US), and South America.⁴

Prevalence rate of adult health check examinees

The HCV prevalence rate in adult health check examinees was reported as 1.7% when tested by 1st-generation enzyme immunoassay (EIA) in early 1990s, just following the discovery of HCV.⁵ The estimated age-standardized prevalence of anti-HCV in the adult (≥ 40 years of age) health check examinees was reported as 1.29% (95% confidence interval 1.12-1.48) and was about 193,000 persons in a collective study including health checkup examinees from Seoul, Ulsan, Jeollanam-do, and Daegu between 1995 and 2000.⁶⁻¹⁰

In 2009, the anti-HCV prevalence rate in health examinations of 291,314 adults ≥ 20 years of age from 29 health examination

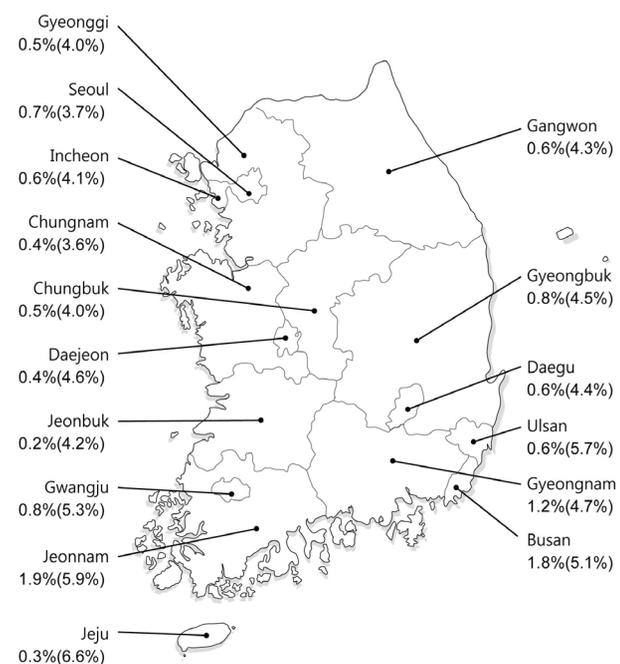


Figure 1. Map of South Korea showing age and sex-adjusted anti-HCV seroprevalence in each area.¹¹

centers was 0.78% using 3rd-generation EIA after adjusting for age, sex, and area.¹¹ The anti-HCV prevalence was higher in women (0.83%) than in men (0.75%) showing an age-related increase with the highest prevalence in those ≥ 60 years of age (20-29 years: 0.34%, 30-39 years: 0.41%, 40-49 years: 0.60%, 50-59 years: 0.80%, 60-69 years: 1.53%, ≥ 70 years: 2.31%). In addition, it varied in different localities; by comparison with the prevalence rate of 0.50-1.20% in most regions including Seoul and Gyeonggi-do, the prevalence rates in Pusan and Jeollanam-do were highest (1.53% and 2.07%, respectively), while Jeju Special Self-Governing Province had the lowest rate of 0.23% (Fig. 1). An update of national HCV prevalence rate in South Korea is expected soon, since the 2012 Korea National Health and Nutrition Examination Survey included anti-HCV testing.

Prevalence of anti-HCV in blood donors, pregnant women, and children

The anti-HCV prevalence rate in 2,040,151 blood donors in 1997 in South Korea was 0.34% as tested by 3rd-generation EIA.¹² From 2005 to 2009, the anti-HCV prevalence in 11,064,532 blood donors was 0.16%, and the HCV RNA-positive rate was 8.4 (0.0084%) of 100,000 donors, among whom 81% were young people aged 10-30 years.¹³

In South Korea, the risk of blood transfusion-related HCV infection decreased from 1 in 81,431 in 2000/2001 to 1 in 2,984,415 after implementation of nucleic acid test for HCV screening of donated blood beginning in February, 2005.¹⁴

The anti-HCV prevalence rates in pregnant women were reported as 0.49-1.7%,¹⁵⁻¹⁷ and a domestic report investigating over 5,000 pregnant women reported rates of 0.42-0.44%.^{18,19} Among anti-HCV-positive pregnant women, 57-60% were positive for HCV RNA.^{18,19}

Domestic studies on HCV prevalence rate in children and adolescents are insufficient. A 0.82% anti-HCV-positive rate tested by 3rd generation EIA in 2,080 children between 6 and 11 years of age living in Seoul was reported.²⁰ However, there have been no other reports or studies on children and adolescents, hindering the accurate assessment of HCV prevalence rate in the pediatric population of South Korea.

Prevalence of anti-HCV in high-risk group

High-risk groups for HCV infection include people with a history of intravenous drug use (IVDU), patients receiving hemodialysis, and those with HIV infection, hemophilia, and leprosy. However, the HCV prevalence rate in these groups has been reported mostly

before 2000, with little data since then.

Domestic anti-HCV prevalence rate in the IVDU group was reported as 48.4-79.2%.²¹⁻²⁴ Among anti-HCV-positive persons, 98.1% were HCV RNA-positive.²⁴ Meanwhile, in case of sharing cocaine suction pipe, the anti-HCV prevalence rate was similar to IVDU group.²⁵

Anti-HCV prevalence rate was 5.9-14.7%^{26,27} in previous studies that included more than 200 patients with chronic kidney diseases and the rate significantly correlated with duration of hemodialysis.

Coinfection rate of HCV was high in those infected with HIV; about 25% of westerners and 5.0-6.3% of HIV-infected individuals in South Korea were coinfecting with HCV.²⁸⁻³⁰

Anti-HCV prevalence rate in 104 hemophilia patients tested by 3rd-generation EIA of was 42.3% in 2002 and the risk of infection correlated with age and severity of hemophilia.³¹ In their 2012 annual report, the Korea Hemophilia Foundation (KHF) reported that 430 of 2,148 (20.0%) hemophilia patients were anti-HCV-positive and 118 of 2,148 (5.5%) were HCV RNA-positive.³²

Leprosy patients can be considered a high-risk group of HCV infection due to their skin lesions and long-term cohabitation in limited areas. The prevalence rate of 96 leprosy patients tested by 2nd-generation EIA was 67.7% in 1997 and 82% of these individuals were immunoblot-positive.³³

Incidence rate of HCV infection

Studies on HCV incidence rate are rare, since only 20-30% of those with acute HCV infection develop symptoms. HCV incidence rates are decreasing in Western countries.³⁴ In the US the incidence rate decreased from 7.4 of 100,000 people from 1982-1989 to 0.7 of 100,000 people from 1994-2006,³⁵ and in Italy, a decreased from 2.02 of 100,000 people in 1996 to 0.55 of 100,000 people in 2006 was reported.³⁶

The HCV infection incidence rate in South Korean blood donors was reported as 13.8 of 100,000 according to a survey conducted on those who donated blood at least twice from 1994-1996.³⁷ The recent HCV infection incidence rates among blood donors who donated at least twice in 2 years between 2000 and 2010 were estimated 6.80 in 2001, 3.19 in 2003, 2.69 in 2005, 1.83 in 2007, and 0.80 in 2009 per 100,000 person-year, showing significant decrease of HCV incidence in this population in South Korea.¹⁴

According to surveillance sample data from the Korea Centers for Disease Control and Prevention (KCDC), the number of reported hepatitis C cases was 1,927 in 2002, 6,407 in 2008, and 4,280 in 2012. Future studies are needed for evaluation of nation-

wide HCV incidence rate in Korea.

Distribution of HCV genotypes

Globally, HCV genotypes 1, 2, and 3 are common and genotypes 4, 5, and 6 are localized to limited regions.^{38,39} Genotype 1a is most common in Northern Europe and North America, and 1b is most common in Far East Asia and Europe. Genotype 2 is less common than genotype 1. Genotype 3 is common in Southeast Asia and genotype 4 is common in the Middle East, Egypt, and Central Africa. Genotype 5 is commonly found in South Africa and genotype 6 is common in Hong Kong, Macau, and Vietnam.

Common HCV genotypes in South Korea are genotype 1b (45-59%) and 2a (26-51%); types 1a, 2b, 3, 4, and 6 are rare genotypes in South Korea.^{40,41}

Whether genotype 1 HCV infection provokes faster progression of hepatic disease than the other genotypes is controversial. A recent meta-analysis reported that genotype 1b patients showed a 1.78-fold higher risk of developing HCC (95% CI, 1.36-2.32) compared to the non-1 genotype patients.⁴² Nevertheless, the HCV genotype is the most crucial factor in determining the efficacy of antiviral therapy; genotypes 1 and 4 result in lower success rates of treatment compared to genotypes 2, 3, and 6.⁴³

PREVENTION

Route of transmission

HCV transmission occurs by parenteral exposure. The main routes of transmission include transfusion of contaminated blood or blood products, organ transplantation, IVDU, unsafe injection or medical procedures, stabs by contaminated syringe or needle, sexual contact with HCV infected person, or perinatal transmission from infected mother to newborns.

Transmission via transfusion was a main route of infection until 1991, but the possibility has become extremely low since a screening test was introduced for blood donors.⁴⁴⁻⁴⁶ The most important route of recent HCV transmission is the use of illicit drugs in developed countries such as the US or Europe; HCV prevalence rate is low,⁴⁷ whereas anti-HCV prevalence in the IVDU group was reported as high as 50-90%.⁴⁸ Meanwhile, unsafe injection with multiple-use medication vials or reused syringes, or unsanitary medical procedures including surgery, endoscopy, and dental treatment without proper disinfection are reported as the

main causes of HCV transmission in developing countries.⁴⁹⁻⁵¹

In addition, meta-analyses have reported that risk factors of HCV transmission include piercing, acupuncture, or tattooing without proper disinfection.⁵²⁻⁵⁴ The HCV infection risk by a small dose of percutaneous exposure, such as needle sticks, is 1.8% (0-7%)⁵⁵⁻⁵⁸ in other countries and 0.92% in South Korea.⁵⁹ Heterosexual persons with chronic HCV infection in long-term monogamous relationships with a partner had little evidence for sexual transmission of HCV. However, the risk becomes higher with multiple sex partners, and unsafe sex including anal sex, sex accompanying wounds, sex carrying other sexually transmitted diseases like HIV, or in homosexuals.^{60,61} The percentage of perinatal transmission was reported as 1-6.2%.^{62,63} It was reported as 1.7% when the mothers were positive for anti-HCV regardless of HCV RNA-positivity, and as 4.3%(3.9-7.1%) in case of HCV RNA-positive mothers.^{63,64} The risk of perinatal transmission increased in female infants, HIV-positive mothers, and mothers with high blood HCV RNA levels.⁶⁵ Cesarean section is reportedly not a preventative method for HCV transmission,^{65,66} and transmission via nursing was very low. Thus, it is not necessary to limit breast-feeding unless nipples are injured or are bleeding.⁶⁷ Reports of horizontal transmission between siblings or family members of HCV infected person are based on a low level of evidence.⁶⁸

A comparative study⁶⁹ of 1,173 HCV patients and 534 control group in five university hospitals between 2007 and 2011 in South Korea reported several independent risk factors of infection including illicit use of drug, needle stick injury, transfusion before 1995, tattoo, and age.⁶⁹

Counselling for prevention

Since an effective vaccine has not been developed, the main strategy of prevention is to educate people on the risk factors for HCV infection and to keep the strict standard for sanitation in every place performing the percutaneous procedures.

HCV infected persons should be counseled not to donate blood, organs, tissues, or semen, and not to share any instrument penetrating skin. They should individually use instruments including toothbrushes, oral hygiene devices, razors, or nail clippers so his/her blood are not exposed to other people. Finger stabbing needles commonly used for Korean home remedy should not be shared. IVDU should be persuaded to stop drug abuse and they should not reuse syringes, needles, injection solution, cotton swab, or alcohol sponges. They must be reminded that other

people can be infected via recklessly disposed needles. Since risk of infection among monogamous couples is very low, use of barrier protections among these couples are not necessarily recommended. Nevertheless, if the partner of the infected individual request or for the infected person with multiple sex partners, it is recommended to use condoms.

Routine screening for HCV is not recommended for all pregnant women. However, for those with a risk factor, prenatal testing for HCV is needed. HCV infection does not mean a restriction of breast-feeding or a recommendation of specific delivery, such as Cesarean section.

Health care facilities should be careful to block HCV transmission. Proper disinfection, cleaning, and management of materials and instruments are essential in medical procedures and invasive procedures including tattooing, piercing, or acupuncture.

[Recommendations]

1. HCV infected persons should not donate blood, organs, tissues, or semen (A1). HCV infected persons should avoid to share toothbrushes, oral hygiene devices, razors, nail clippers, or any instrument penetrating skin, so as not to expose his/her blood to other people (C1).

2. Intravenous drug abusers should be counseled to stop illicit drug abuse (A1). They should be educated about routes of infection and tested regularly for HCV infection (B1).

3. Proper disinfection, cleaning, and management of materials and instruments are essential in medical procedures and invasive procedures including tattooing, piercing, or acupuncture (B1).

4. Since risk of infection among monogamous sexual partners is very low, use of barrier protection is not advised in these couples (B1). However, for those with multiple sex partners, it is recommended to use condoms (B1).

5. For pregnant women, if a risk factor for HCV infection is detected or HCV infection is suspected otherwise, prenatal testing for HCV infection is recommended (B1). HCV infection does not mean a restriction of breast-feeding or a recommendation of specific delivery, such as Cesarean section (B2).

NATURAL HISTORY

Acute HCV infection

After 1-3 weeks of HCV infection, HCV RNA becomes detectable in blood and rapidly increases.^{70,71} Serum alanine transaminase (ALT) level increases due to hepatocyte damage after 4-12 weeks of the infection. Most infection is asymptomatic (70-80%) but symptoms including flu-like symptoms, fatigue, vomiting, nausea, right upper quadrant pain, muscle pain, or pruritus may develop within 2-12 weeks. About 20% of acute infection accompanies jaundice with serum bilirubin level below 3-8 mg/dL, and acute liver failure occurs rarely in <1% of cases. Acute hepatitis progressed to chronic infection in 54-85% of patients and 20-50% of patients recovered spontaneously within 3-4 months.⁷²⁻⁷⁴ Spontaneous recovery rate is different depending on route of infection; spontaneous recovery rate in post-transfusion cases was 12%, while in the cases not related to transfusion it was 29-52%.⁷⁴⁻⁷⁶ Factors related to spontaneous recovery are hepatitis accompanying jaundice, female, low viral load, and genotype 3.⁷⁵⁻⁷⁷ A Korean study reported that among 18 acute hepatitis C patients (17 patients showed symptoms), 12 patients spontaneously recovered and 6 patients progressed to chronic hepatitis.⁷⁸ Another study including 47 patients of acute hepatitis C enrolled in seven Korean institutions showed that mean age of 45.8 years, 21 of 47 (44.7%) patients recovered spontaneously, and 16 patients received antiviral therapy. All 12 patients who were treated and followed-up patients achieved a sustained virological response (SVR). Ten patients who did not receive antiviral therapy progressed to chronic hepatitis.⁷⁹

A single nucleotide polymorphism (SNP) of the interleukin 28B (IL 28B) gene is strongly related to spontaneous recovery from acute hepatitis C infection.⁸⁰⁻⁸² IL28B is located on chromosome 19 and expresses interferon-lambda-3. A study reported a spontaneous recovery rate of 53% in case with genotype CC of IL28B SNP rs12979860 and of 28% in genotype CT or TT (Odds ratio (OR)=0.33, $P<10^{-12}$).⁸³ However, future studies are needed since there have been no Korean studies of IL28B SNP in acute HCV infection.

Chronic HCV infection

About 50-80% of HCV infected patients progress to chronic infection. Once it becomes chronic hepatitis, it can cause persistent liver injury without spontaneous recovery leading to

cirrhosis and HCC. Most (60-80%) patients with chronic hepatitis show no symptoms, but some can experience abdominal discomfort, fatigue, nausea, muscle pain, arthritis, or weight loss. About 60-70% of chronic HCV infected patients show chronic hepatitis accompanying steady or intermittent elevation of serum ALT. About 15-56% of chronic hepatitis may progress to cirrhosis through a period of 20-25 years.^{71,84-86} Among patients with liver cirrhosis, the annual incidence of HCC is reported as 1-4.9%,⁸⁷⁻⁸⁹ that of decompensated liver cirrhosis is 3-6%,^{71,88-90} and the overall annual mortality rate is 2-4%. An observational study including 1,137 Korean chronic HCV infected patients for an average follow-up of 55.2 months reported a 14.2% rate of disease progression, defined as development of HCC, spontaneous bacterial peritonitis, variceal bleeding, hepatic encephalopathy, and death due to hepatic diseases, and overall annual mortality rate was 2.0-2.5%.⁹¹ Cumulative probability of disease progression was 6.3%, 12.9%, and 26.1% at 1, 2, and 3 years, respectively. From 1,137 patients, 490 (43.0%) received antiviral treatment and 60.4% showed an SVR. Chronic infection without antiviral treatment showed significantly higher risk of disease progression compared to chronic infection with antiviral treatment (37.4% vs. 10.7%, respectively, $P < 0.05$). A 5-year cumulative probability of disease progression was higher in a non-SVR group compared to group with SVR (13.0% vs. 3.7%, respectively, $P < 0.05$).

Factors affecting disease progression include duration of infection, age at the time of infection (≥ 40 years of age), male, alcohol intake, coinfection with other viruses (HBV, HIV), insulin resistance, obesity, immune-depressed patients, organ transplantees, elevation of ALT, or genetic factors such as IL28B.⁷¹ Excessive alcohol intake by chronic hepatitis C patients is strongly related to occurrence of cirrhosis, and increases risk of HCC.^{86,92-95} Fatty liver, insulin resistance, and obesity increase risks of hepatic fibrosis and HCC development in chronic hepatitis C patients.⁹⁶⁻⁹⁹

Coinfection of HIV or HBV in chronic HCV infection causes faster progression of liver diseases and increases the risk of HCC compared to HCV single infection.¹⁰⁰⁻¹⁰² In addition, coinfection of hepatitis A virus (HAV) in chronic hepatitis C increases the risk of hepatic failure.¹⁰³ Pathologic stage of hepatic fibrosis at the time of chronic hepatitis C diagnosis is the most important predictor for progression to cirrhosis (refer to the Diagnosis section of this manuscript).^{86,100} Stage 1 hepatic fibrosis has a 10-30% incidence rate of cirrhosis over a period of 15 years, while most cases of stage 3 hepatic fibrosis are expected to progress to cirrhosis within 15 years. Therefore, patients diagnosed as having hepatic fibrosis over stage 2 must be considered for active antiviral treatment.

[Recommendations]

6. Continuous management and surveillance for development of cirrhosis and HCC is necessary in chronic hepatitis C patients (A1).

7. Chronic hepatitis C patients are recommended abstinence from alcohol or moderation in drinking, and to maintain suitable body weight through physical exercise and dietary control, since disease progression is related to alcohol, obesity, or insulin resistance (B1).

8. Patients with chronic HCV infection without antibodies against HAV and HBV should be vaccinated for HAV and HBV (C1).

DIAGNOSIS OF HCV INFECTION AND ASSESSMENT OF LIVER DISEASE SEVERITY

Biochemical tests, serologic assays, and HCV RNA testing are

Table 2. Interpretation of HCV assays¹¹⁴

Anti-HCV	HCV RNA	Interpretation	Further evaluation
Positive	Positive	Acute hepatitis C	
		Chronic hepatitis C	
Positive	Negative	Resolution of HCV infection	Recheck anti-HCV & HCV RNA, 3-6 months later
		Acute HCV infection during period of low-level viremia	
		False positive anti-HCV test	
		False negative HCV RNA test	
Negative	Positive	Early acute HCV infection	Recheck anti-HCV & HCV RNA, 3-6 months later
		Chronic HCV infection in setting of immunosuppressed state	
		False positive HCV RNA test	

needed to confirm HCV infection. Physical examination and history taking should be done to understand the routes of transmission and block further reinfection. HCV genotyping is essential for treatment and radiologic examination, liver biopsy, or noninvasive evaluation of hepatic fibrosis can be done to determine necessity of treatment, and to assess liver disease severity. Interpretation of serological and virological test results is summarized in Table 2.

DIAGNOSIS

Serologic assays

Anti-HCV

Detection of anti-HCV in serum or plasma is used for screening of a high risk group and for diagnosis of acute or chronic hepatitis C.¹⁰⁴ The 3rd generation EIA uses recombinant antigens including core, NS3, NS4, and NS5 of HCV protein, and its sensitivity and specificity are 97.2-99% and 99.8-100%, respectively, when tested in immune-competent individuals.¹⁰⁵⁻¹⁰⁷ If signal/cutoff (S/CO) ratios of 3rd generation EIA exceed 3.8, a positive result will be apparent in 95% of recombinant immunoblot assay (RIBA).¹⁰⁸⁻¹¹⁰ However, a cutoff level of S/CO ratios can be different according to the types of equipment, so that high S/CO ratios do not always mean true positive.¹¹¹ Recently, use of enhanced chemiluminescent immunoassay (CLIA) or electrochemiluminescence immunoassay (ECLIA) is increasing since those assays detect antigen-antibody reaction more sensitively compared to 3rd generation EIA. Meanwhile, there is point-of-care tests using saliva or fingerstick blood producing rapid results within 20 minutes.¹¹²

Average time between infection and seroconversion of anti-HCV is 8-9 weeks and anti-HCV is detectable in >97% of patients with HCV infection within 6 months.^{113,114} Anti-HCV is not a neutralizing antibody and persists indefinitely in chronic hepatitis C patients or even after recovery. Therefore, the differentiation of current infection from the past infection after recovery is impossible using anti-HCV positivity. Negative result for anti-HCV in combination with a positive result for HCV RNA may represent early state of acute infection, chronic infection in the setting of severe immunosuppressed condition, such as patients on hemodialysis, HIV coinfection, solid organ transplantation recipients, hypo-/a-gammaglobulinemia, and patients with HCV-associated essential mixed cryoglobulinemia.^{3,105,115} In these patients, HCV RNA testing is necessary for diagnosis of HCV infection. On the other hand, false-positive result for anti-HCV with negative result

for HCV RNA can occur in patients with autoimmune diseases.¹¹⁶

Recombinant immunoblot assay (RIBA)

RIBA detects 4 HCV-specific antibodies on nitrocellulose strips.¹¹⁴ Borderline positive results of anti-HCV using EIA or CLIA test can be confirmed with RIBA, but RIBA has low sensitivity despite high specificity.^{110,117} Recently, clinical role of RIBA has disappeared because validated HCV RNA assays are sequentially conducted in patients showing positive result for anti-HCV to confirm HCV infection.

Virological assays

HCV RNA assays

HCV RNA assays are classified as quantitative and qualitative assays. Since the detection cutoff of qualitative assays is 50 IU/mL and more sensitive than previous generation quantitative assays, HCV RNA qualitative assays had been used as a diagnostic confirmation of HCV infection and HCV RNA quantification is used for pretreatment assessment and monitoring of virological response during and after antiviral therapy.^{104,110,118} However, recently available quantitative HCV RNA assays are using real-time polymerase chain reaction (PCR) and transcription-mediated amplification (TMA), and are very sensitive with lower detection limit of 12-15 IU/mL, while they have a broad measuring range with upper limit of 7-8 log IU/mL with 98-99% of diagnostic specificity independent of HCV genotype.^{104,119-124} Therefore, quantitative HCV RNA tests are now widely used both for diagnosis and evaluation of treatment response.^{125,126}

In 1997, the World Health Organization established an international standard for HCV RNA quantification unit, IU, rather than HCV copy numbers.^{127,128} However, since different laboratories can vary in viral quantification results,¹²⁹ it is recommended to use the same laboratory test before, during, and after-treatment for monitoring, if possible.^{114,125}

Blood HCV RNA is detectable as early as 2 weeks after infection,⁷⁴ rapidly increases to reach a plateau, and decreases along with ALT after ALT attains a maximum level.¹³⁰ HCV RNA levels maintain a steady state in patients with chronic hepatitis C.^{130,131} HCV RNA levels do not significantly correlated with the severity of hepatic inflammation or fibrosis, and show little changes during chronic infection state without antiviral treatment.^{132,133}

Genotyping assays

HCV genotyping is useful for epidemiologic studies as well as for predicting treatment response. Therefore, HCV genotype should be assessed before treatment for determining the optimal therapeutic duration and dose of ribavirin.¹³⁴ HCV is classified into six major genotypes (1-6) and is subdivided into subtypes identified by lower-case letters, such as 1a or 1b. Differences of 31-33% at the nucleotide level among each genotype, compared with 20-25% among each subtype.¹³⁵ HCV genotype does not change within a same person unless otherwise reinfected.

Determining HCV genotypes and subtypes can be performed by using direct sequence analysis, reverse hybridization, or restriction fragment mass polymorphism (RFMP).¹³⁶ Most genotyping assays analyze 5'-untranslated region (UTR) and HCV core regions where nucleotide sequences are highly conserved.¹³⁷ With analysis of 5'-UTR region, HCV genotyping errors occur at a rate of <3%, but HCV subtyping errors may occur in 10-25%; especially, this assay does not accurately discriminate between subtype 1a and 1b.¹³⁸⁻¹⁴⁰ Subtyping is not necessary in antiviral therapy using interferon alpha and ribavirin combination, but in the treatment including DAAs, subtypes may need to be confirmed since DAAs act differently according to genotype 1a and 1b.¹⁴⁰ Genotyping is not possible in <5% of the patients. This results from low HCV levels, problems with the PCR amplification process, or high nucleotide variability of HCV genome itself.¹⁴¹

HCV drug-resistance mutation tests

HCV drug-resistance test has not been performed clinically, unlike cases with hepatitis B virus infection. As various DAAs are being used with improvement of outcomes of treatment, drug resistance tests for these drugs may be needed in the future.¹⁴²

Screening test for HCV infection

Routine screening for HCV infection is recommended in populations at risk, such as those with a history of blood transfusions or organ transplantation prior to 1992; persons who have injected illicit drug; persons with HIV infection, hemophilia, or Hansen's disease; persons who have been on hemodialysis; children born to mothers infected with HCV; and health care providers after a needle stick injury or mucosal exposure to HCV positive blood (Table 3).¹¹⁴ In 2012, the US Centers for Disease Control and Prevention expanded the screening population to the birth cohort born between 1945-1965 and recommended to screen for HCV once in a lifetime, considering cost effectiveness.¹⁴³⁻¹⁴⁵ A Japanese study revealed that the strategy of hepatitis C screening appears cost-effective in the general population as well as in the high-risk group,¹⁴⁶ but an European study showed that the screening test for general population is cost-effective only in HCV prevalent areas.¹⁴⁷ Therefore, since the epidemiologic characteristics and health care system differ between nations, to adapt the optimal screening strategy in Korea, further research on its cost effectiveness is urgently needed.

Diagnosis in case of accidental exposure

The average incidence of anti-HCV seroconversion in healthcare providers after accidental percutaneous exposure from HCV-infected blood was reported to be 1.8% (0-7%) in other countries^{57,58,148-152} and 0.92% in South Korea.⁵⁹ When a person is exposed to HCV-positive source, baseline testing for anti-HCV and serum ALT level should be performed. If anti-HCV is negative, HCV RNA assay should be performed 4-6 weeks after exposure for early diagnosis. Even if baseline tests for HCV infection were all

Table 3. Persons for whom HCV screening is recommended¹¹⁴

Persons suspected of having acute or chronic HCV infection
Persons who have received blood/blood products transfusions or organ transplants prior to screening program
Persons who have ever injected illicit drugs
Persons who have ever been on hemodialysis
Persons with HIV infection
Persons with hemophilia
Persons who have current sexual contact with HCV-infected persons*
Children born to mothers infected with HCV
Health care providers after a needle stick injury or mucosal exposure to HCV positive blood

*The prevalence of infection is low.

negative, follow-up testing for anti-HCV and serum ALT level should be performed 4-6 months after the exposure.^{125,149} If anti-HCV is positive, a confirmative test is needed.

ASSESSMENT OF LIVER DISEASE SEVERITY

To decide the treatment for HCV infected patients, the severity of the liver disease must be evaluated through liver biopsy and/or noninvasive tests. It is important to confirm whether the patient has liver cirrhosis or not before treatment since existence of liver cirrhosis can make difference in the treatment response, its prognosis, and necessity of surveillance for HCC.

Liver biopsy

Liver biopsy is assessed for grade and stage of the hepatic injury.^{114,153} The Metavir¹⁵⁴ and Ishak¹⁵⁵ scoring systems are most widely used, and the scoring system proposed by the South Korean Study Group for the Pathology of Digestive Diseases is used in South Korea (Table 4).¹⁵⁶ Although liver biopsy is not mandatory prior to treatment, it can help to determine when to start treatment and to provide information regarding the treatment response and prognosis. Considering the natural history of the disease, the cost of treatment and its possible adverse effects, treatment can be postponed if liver histopathology shows minimal to moderate fibrosis state <2 (Metavir stage 2 or periportal fibrosis of the South Korean Study Group for the Pathology of Digestive Diseases, F2).^{74,157,158} In this case, a liver

biopsy should be repeated at 4-5 years later to reassess the necessity of treatment according to the progression speed of liver disease.¹⁵⁹ About 5-30% of patients with genotype 1 with consistently normal serum ALT may have severe fibrosis¹⁶⁰⁻¹⁶³ and liver biopsy would be useful to determine treatment initiation in this group.^{86,164,165} Even though hepatic steatosis^{153,166,167} and liver iron load overload¹⁶⁸ might impede treatment response, presence of these findings is not the contraindication of treatment.¹⁶⁹⁻¹⁷¹ If the liver biopsy is not conducted and treatment is not undertaken, continuous monitoring is needed. Liver biopsy and start of treatment should be considered when there is elevation of serum ALT level and evidence of liver disease progression.¹¹⁴

Noninvasive tests for evaluation of liver fibrosis

Even though liver biopsy has been widely accepted as a gold standard test for evaluation of liver fibrosis,^{172,173} it can cause serious complications^{174,175} and sampling errors,¹⁷⁶ and it requires histopathologic specialist for accurate interpretation and also medical costs. Therefore, various blood marker panels have been developed including aspartate aminotransferase (AST)-platelet ratio index (APRI) and AST/ALT ratio (AAR), and Forns' index that use combination of AST, ALT, prothrombin time, platelet, and cholesterol; FibroTest, Hepascore, FibroMeter that use indirect fibrosis markers, such as α -2 macroglobulin and haptoglobin; FibroSpect II and Enhanced Liver Fibrosis test that use direct fibrosis markers, such as hyaluronic acid and tissue inhibitor of matrix metalloproteinase-1.¹⁷⁷⁻¹⁸⁸

APRI is calculated by the formula (AST/upper limit of normal for

Table 4. Comparison of scoring systems for histological stage¹¹⁴

Stage	Metavir ¹⁵⁴	Ishak ¹⁵⁵	The Gastrointestinal Pathology Study Group of Korean Society of Pathologists ¹⁵⁶
0	No fibrosis	No fibrosis	No fibrosis (F0)
1	Periportal fibrotic expansion	Fibrous expansion of some portal areas with or without short fibrous septa	Portal fibrosis (F1)
2	Periportal septae 1 (septum)	Fibrous expansion of most portal areas with or without short fibrous septa	Periportal fibrosis (F2)
3	Porto-central septae	Fibrous expansion of most portal areas with occasional portal to portal bridging	Septal fibrosis (F3)
4	Cirrhosis	Fibrous expansion of most portal areas with marked bridging (portal to portal and portal to central)	Cirrhosis (F4)
5		Marked bridging (portal to portal and portal to central) with occasional nodules (incomplete cirrhosis)	
6		Cirrhosis	

AST) \times 100/platelet count ($\times 10^9/L$). The APRI is shown to be accurate in predicting both significant fibrosis (Ishak score ≥ 3) defined as APRI >1.5 (AUROC=0.8) and cirrhosis defined as APRI >2 (AUROC=0.89).¹⁸⁹ A normal value of AAR is <0.8 , but it increases along with hepatic fibrosis progression, so that AAR value >1.0 has a 73.7-100% positive predictive value in diagnosis.^{182,190,191}

Liver stiffness measurement using transient elastography can be used to assess hepatic fibrosis,¹⁹²⁻¹⁹⁵ although it is not approved by the Food and Drug Administration as of 2013. Transient elastography cannot totally replace liver biopsy, because it often cannot produce reliable measurements in obese patients, and tends to give falsely high results in cases of acute hepatitis with severe inflammation and necrosis with mild fibrosis.^{196,197} In case of chronic hepatitis C, cutoff values determining significant fibrosis ($\geq F2$) vary from study-to-study, ranging from 7.1 to 8.8 kPa, with an AUROC of 0.79-0.83.¹⁹⁸ The AUROC of transient elastography for diagnosis of liver cirrhosis ranged from 0.95-0.97, with cutoff value of 12.5-14.6 kPa (77-78% positive predictive value, 95-97% negative predictive value).^{177,184,192,198-202}

Other newly developed noninvasive tests include acoustic radiation force impulse (ARFI) imaging, real time elastography, magnetic resonance (MR) elastography, diffusion-weighted MR image, and MR spectroscopy. However, validations of their effectiveness are still needed.²⁰³⁻²⁰⁵

[Recommendations]

9. Anti-HCV should be tested in patients suspected of having acute or chronic HCV infection (A2).

10. HCV RNA should be tested in patients with a positive anti-HCV test for the purpose of confirmative diagnosis (A1).

11. Even with negative anti-HCV, HCV RNA testing is required when acute HCV infection is suspected or in the presence of unexplained liver disease in immunosuppressed patients (B1).

12. HCV RNA quantitative assay and genotyping should be performed prior to antiviral treatment (A1).

13. As soon as being exposed to infected blood or body fluid, testing of anti-HCV and serum ALT level should be performed. If the test result of anti-HCV is negative, HCV RNA assay is to be conducted 4-6 weeks after the exposure for early diagnosis. Even if baseline tests were all negative, follow-up testing for anti-HCV and serum

ALT level should be done 4-6 months after the exposure (B2).

14. Assessment of liver disease severity is essential prior to antiviral treatment (B1).

15. Liver biopsy (B2) and/or noninvasive test for assessment of hepatic fibrosis (C2) can be done to make treatment decision and to predict prognosis.

TREATMENT GOALS

The goals of hepatitis C treatment are to eradicate HCV and to prevent complications and mortality from liver cirrhosis and HCC. It is difficult to evaluate the treatment goal in a short period of time due to slow evolution of chronic hepatitis C over several decades. Therefore, the short-term goal of hepatitis C treatment is to achieve an SVR defined as undetectable serum HCV RNA by a sensitive assay with a lower limit of detection <50 IU/mL at 24 weeks after the end of treatment. Since HCV does not reappear in 99% of the patients who achieve SVR,^{206,207} SVR is considered as actual eradication of HCV. In $>90\%$ of patients who achieve SVR, histological hepatic fibrosis improves or at least does not get worse,^{208,209} complications of cirrhosis significantly decrease,²¹⁰ occurrence of hepatocellular carcinoma decreases,^{211,212} and survival rate improves.^{213,214}

[Recommendations]

16. The goals of hepatitis C treatment are to eradicate HCV and to prevent complications and mortality from liver cirrhosis and hepatocellular carcinoma. (A1).

17. A short-term goal of hepatitis C treatment is to achieve an SVR defined as an undetectable serum HCV RNA by a sensitive assay with a lower limit of detection <50 IU/mL at 24 weeks after the end of treatment (A1).

INDICATIONS FOR TREATMENT

All hepatitis C patients who have no contraindications to treatment can be considered for antiviral treatment. However, treatment would be applicable in cases where benefits of treatment outweigh the risks of treatment. Generally, treatment is recommended for patients with significant hepatic fibrosis (\geq stage F2), and initiation of treatment for those with advanced

fibrosis (stage F3-4) is required as soon as possible. In case of mild hepatic fibrosis, treatment can be delayed after considering patient age, willingness for treatment, or perspectives of new drugs.

Absolute contraindications to the combination therapy of peginterferon alpha and ribavirin are summarized in Table 5.

Treatment should be individualized considering benefits and risks in cases of decompensated cirrhosis, liver transplant recipients, current users of illicit drugs or alcohol, chronic renal diseases, coinfection with HIV, and no or mild fibrosis on liver biopsy (Table 6). The criteria of contraindications or individualization may change, since DAAs that are more efficient with fewer adverse effects are expected to be adapted to practice in the future.

A persistently normal ALT is defined as ALT value <40 IU/mL on two to three occasions separated by at least a month over a period of 6 months. Patients with persistently normal ALT have milder fibrosis compared to patients with abnormal ALT on average,^{215,216} but about 5-30% of patients with persistently normal ALT have advanced fibrosis and cirrhosis.²¹⁷⁻²¹⁹ A Korean study reported that some untreated patients with persistently normal ALT had progressive liver disease, and the risk of progressive liver disease was higher in patients with ALT value >23 IU/mL.²²⁰ Therefore, it is necessary to redefine the normal range of ALT and to treat patients with advanced fibrosis more actively, regardless ALT value. The SVR rate of normal ALT groups is similar to that of abnormal ALT groups.^{221,222}

The elderly (>65 years of age) often have advanced liver diseases with higher necessity of treatment,²²³ but the SVR rates are lower and the adverse effects are more frequent.^{224,225} However, treatment of elderly hepatitis C patients can decrease the incidence rate of HCC and increase the survival rate.^{226,227} A recent study reported that the SVR rate in patients >60 years of age is similar to that of patients in 50-59 years of age.^{228,229} Little

data are available concerning treatment in those >70 years of age. The decision of treatment in the elderly follows general rules.

[Recommendations]

18. All HCV-infected patients with no contraindications to treatment are considered as targets of treatment (A2).

19. Treatment should be individualized under overall consideration of the severity of liver diseases, chance of treatment success, risks of severe adverse effects, status of accompanying diseases, and patient willingness for treatment (B1).

DEFINITION OF TREATMENT RESPONSE

The combination therapy of peginterferon alpha and ribavirin has considerable cost and adverse effects. Meanwhile, the likelihood of SVR gets higher as the time of HCV RNA disappearance during the therapy is shorter.²³⁰ Response-guided therapy is a strategy to modify the duration of treatment based on the time of HCV RNA disappearance by measuring serum HCV RNA at weeks 4, 12, and 24 of treatment.

Table 6. Persons for whom therapy should be individualized¹¹⁴

Acute hepatitis C
No or mild fibrosis on liver biopsy
Decompensated cirrhosis
Liver transplant recipients
Current users of illicit drugs or alcohol
Chronic renal disease
Co-infection with HIV
Age <18 years

Table 5. Contraindications to treatment with peginterferon alpha and ribavirin¹¹⁴

Uncontrolled psychiatric illness or depression
Uncontrolled autoimmune disease
Transplantation of solid organ except liver
Untreated thyroid illness
Pregnancy or unwilling to comply with adequate contraception
Severe concurrent medical illness, such as poorly controlled hypertension, heart failure, significant coronary heart disease, poorly controlled diabetes mellitus, and chronic obstructive pulmonary disease
Age ≤ 2 years
Hypersensitivity to peginterferon alpha or ribavirin

A rapid virological response (RVR) is defined as undetectable HCV RNA by a sensitive assay with lower limit of detection <50 IU/mL at week 4 of treatment. The SVR rate is expected to be 87.5-100% in HCV genotype 1 patients with a RVR and to be 33.3-63.8% in those without a RVR.²³¹⁻²³³ The SVR rate is expected to be 85-86.5% in HCV genotype 2 and 3 patients with a RVR, and 54-58.3% in those without a RVR.^{232,234}

An early virological response (EVR) is defined as undetectable HCV RNA using a sensitive assay with a lower limit of detection <50 IU/mL, or ≥ 2 log reduction of HCV RNA compared with the baseline level. The SVR rate is as low as 3% in HCV genotype 1 patients without an EVR.²³⁵⁻²³⁷ Therefore, medical costs and adverse effects can be reduced by discontinuing therapy in cases without an EVR. An EVR is classified as a complete EVR (cEVR) defined as undetectable HCV RNA and a partial EVR (pEVR) defined as an EVR with detectable HCV RNA at week 12. A delayed virological response (DVR) is defined as a pEVR that eventually resulted in undetectable HCV RNA at week 24.^{238,239} A null response is defined as <2 log reduction of HCV RNA level from baseline at week 12 of therapy, whereas partial nonresponse is defined as ≥ 2 log reduction of HCV RNA level from baseline but detectable HCV RNA at week 12 and 24.

An end-of- treatment response (ETR) is defined as undetectable HCV RNA at the end of treatment using a sensitive assay with a

lower limit of detection <50 IU/mL. SVR is defined as undetectable HCV RNA by a sensitive assay with a lower limit of detection <50 IU/mL at 24 weeks after the cessation of treatment. A SVR evaluated at 12 weeks (SVR12) after the end of treatment is reported to be almost identical to a SVR at 24 weeks after the cessation of treatment,²⁴⁰ and recent clinical trials for new drugs tend to evaluate therapeutic efficacy by a SVR12. Viral breakthrough refers to the reappearance of HCV RNA during the treatment after virological response, and relapse is defined as the reappearance of HCV RNA after treatment is discontinued (Table 7).

[Recommendations]

20. HCV RNA in blood should be measured at weeks 4, 12, and 24 of treatment depending on HCV genotype to

Table 8. Predictors of SVR

Pretreatment Predictors	On-treatment Predictors
Genotype	RVR
IL28B polymorphism	EVR
Stage of fibrosis	Treatment adherence
HCV RNA levels	
Age, Ethnicity, Insulin resistance, Obesity	

Table 7. Definitions of virological responses during therapy^{114,125}

Virological response	Definition	Clinical implication
Rapid virological response (RVR)	Undetectable HCV RNA (<50 IU/mL) at week 4 of therapy	May allow shortening of course for genotypes 2&3 and possibly genotype 1 with low viral load
Early virological response (EVR)	≥ 2 log reduction of HCV RNA level from baseline at week 12 of therapy	Negative predictor of SVR
Complete EVR (cEVR)	Undetectable HCV RNA at week 12 of therapy	
Partial EVR (pEVR)	EVR but detectable HCV RNA at week 12 of therapy	
Delayed virological response (DVR)	≥ 2 log reduction of HCV RNA level from baseline but detectable HCV RNA at week 12 and undetectable HCV RNA at week 24	
End of treatment response (ETR)	Undetectable HCV RNA at the end of 24 or 48 weeks of treatment	
Sustained virological response (SVR)	Undetectable HCV RNA (<50 IU/mL) at 24 weeks after treatment	Best predictor of a long-term response to treatment
Null response (NR)	<2 log reduction of HCV RNA level from baseline at week 12 of therapy	
Partial nonresponse	≥ 2 log reduction of HCV RNA level from baseline but detectable HCV RNA at week 12 and 24	
Breakthrough	Reappearance of HCV RNA in serum during treatment after virological response	
Relapse	Reappearance of HCV RNA after treatment is discontinued	

evaluate individual therapeutic responses and to modify the duration of treatment (B1).

21. HCV RNA should be measured at the end of treatment and 24 weeks after the cessation of treatment to evaluate therapeutic effects and to identify the achievement of SVR (A1).

PREDICTORS OF TREATMENT RESPONSES

Predicting the likelihood of SVR is helpful for each patient's decision to initiate therapy (Table 8). Strongest pretreatment predictors for SVR include HCV genotype,^{235,241,242} degree of hepatic fibrosis,²⁴³ and IL28B polymorphism.^{243,244} The SVR rates are 40-60% in HCV genotype 1 patients whereas they are about 70-80% in HCV genotype 2 and 3 patients.^{235,245} Patients with F0-F2 fibrosis have 2.7-times higher SVR rates compared to those with F3-F4 fibrosis.²⁴³ The SVR rates are higher by 2.4-2.7 times in patients with a viral load <400,000-800,000 IU/mL compared to those with a viral load exceeding 800,000 IU/mL.^{231,243,246} The SVR rates decrease with conditions including old age (>40 years of age),²³⁵ African-Americans,²⁴⁷ body weight over 70 kg,^{235,241} and insulin resistance.^{248,249}

Recent studies have revealed that host IL28B polymorphism is a strong predictor for SVR.^{243,244,250} SVR rates vary depending on SNP of IL28B; in other words, C or T allele of the rs12979869 locus. The SVR rates of HCV genotype 1 Caucasian patients are 69%, 33%, and 27% in CC homozygote, CT heterozygote, and TT homozygote, respectively. The SVR rates of HCV genotype 1 African-American patients are 48%, 15%, and 13%, respectively.^{243,250} The SVR rates of HCV genotype 1 Korean patients are 73-88% in CC homozygote and 0-40% in CT heterozygote.²⁵¹⁻²⁵³ IL28B polymorphism is variable depending on race. CC homozygote population in Korea accounts for 88-89%,²⁵¹⁻²⁵³ compared to 17% in African-Americans and 37% in Caucasians²⁴³. Further study is needed to evaluate the usefulness of pretreatment determination of IL28B polymorphism in Korea, where about 90% of the population has the CC homozygote, although many institutions in western countries determine IL28B polymorphisms to predict SVR prior to the initiation of treatment. Polymorphism of the rs8099917 locus near IL28B also affects SVR, and a SVR rate is higher in the TT or TG genotype than in the GG genotype.²⁵⁴

RVR is the strongest on-treatment predictor for SVR,^{231,232} and the likelihood of a SVR increases by 9-times with a RVR.²⁴³ Meanwhile, an EVR is a strong negative predictor for a SVR and the SVR rate

is very low (3%) without an EVR.²³⁶ In addition, SVR increases when medication adherence exceeds 80%,²⁵⁵ so efforts to assess and maintain the medication adherence can increase the SVR rate.

TREATMENT OF CHRONIC HEPATITIS C

Treatment of hepatitis C is rapidly evolving. SVR rates have increased from about 10% with conventional interferon monotherapy for 6 months, to about 54-56% with combination therapy of peginterferon alpha and ribavirin, and further to 75% with triple therapy in which boceprevir or telaprevir is added to the peginterferon alpha and ribavirin combination therapy.^{235,241,256-259}

In South Korea, the dual combination therapy of peginterferon alpha and ribavirin has been the standard therapy in 2013, since DAA is still not approved for practice. Response-guided therapy is used to reduce adverse effects and to increase therapeutic effects. It is expected that drugs including DAAs with a strong antiviral effect and relatively few adverse effects will be introduced soon in South Korea. DAA acts on a specific step of viral life cycle. DAAs including NS3/4A protease inhibitors, NS5A inhibitors, and NS5B polymerase inhibitors and host-targeting antiviral agents, such as the cyclophilin A inhibitor and miR-122, are under development. It is expected that triple or quadruple therapy in which one or two DAAs plus peginterferon alpha and ribavirin, or interferon-free therapy with combination of oral agents would be available soon.^{260,261} Nearly 90% of a SVR rate and shortening of treatment duration with those new therapeutic strategies have been reported,^{262,263} although more evidence is needed. However, the high cost of the drugs, drug resistance, drug interactions, and new adverse effects must be considered.

TREATMENT OF GENOTYPES 1 AND 4 CHRONIC HEPATITIS C

Optimal treatment of genotypes 1 and 4

The standard of care for HCV genotypes 1 and 4 infected patients in 2013 in South Korea is combination therapy of peginterferon alpha and ribavirin for 48 weeks.^{235,241,242} Currently, two types of peginterferon alpha are approved for the treatment of chronic hepatitis C: peginterferon alpha-2a (pegasys; Hoffman-La Roche, USA) and peginterferon alpha-2b (peg-Intron; MSD, USA). Peginterferon alpha is a polyethylene glycol (PEG)-modified inter-

feron alpha (40 kD PEG for peginterferon alpha-2a, 12 kD PEG for peginterferon alpha-2b), which has a longer half-life and higher blood concentration for an extended period of time. Therefore, peginterferon alpha is more effective and is more convenient for once-weekly injection compared to thrice-weekly injections of conventional interferon alpha.²⁶⁴ Peginterferon alpha-2a should be injected at a uniform dose of 180 µg once a week, regardless of the patient body weight, whereas peginterferon alpha-2b is to be injected at a dose of 1.5 µg/kg once a week. Ribavirin is to be given in weight-based dose. Most studies suggested 1,000 mg/day of ribavirin in patients with a body weight under 75 kg and 1,200 mg/day for a body weight over 75 kg when given with peginterferon alpha-2a, and 800 mg/day of ribavirin for bodyweight <65 kg, 1,000 mg/day for 65-80 kg, 1,200 mg/day for 85-105 kg, and 1,400 mg/d for >105 kg when given with peginterferon alpha-2b.

SVR rates in Europe and the US were reported as 40-50% when HCV genotype 1 patients were treated with peginterferon alpha and ribavirin.²⁶⁵ SVR rates in South Korea were reportedly higher; 53.6-69.5%^{228,245,266-268} and 62.7% in pooled analysis of 10 studies.²⁶⁹ This is related to the higher frequency of favorable IL28B genotypes in Koreans than in Whites or Blacks.^{81,244,252,254,270,271}

Standard of care for HCV genotype 4 infected patients is the combination therapy of peginterferon alpha and ribavirin for 48 weeks, the same as the standard of care for HCV genotype 1. SVR rate was reported as 72%.²⁷² There are no reports on therapeutic outcome for chronic HCV genotype 4 in South Korea.

Response-guided therapy in genotypes 1 and 4

Several studies have investigated whether treatment duration could be shortened from 48 to 24 weeks when a RVR is achieved using combination therapy of peginterferon alpha and ribavirin for HCV genotype 1 patients. SVR rates of 24- and 48-week treatment groups were 77.2-100% and 85-92.4%, respectively,^{230,231,273-276} which were not statistically significant. However, the upper limit of lower level of HCV RNA concentration was inconsistent, ranging from 400,000 to 800,000 IU/mL and the number of recruited patients was not large enough in those studies. Recently, two meta-analyses of randomized controlled studies including the patients with a RVR showed that a lower rate of SVR and higher recurrence rate were observed in the 24-week treatment group when compared with that in the 48-week treatment group. However, in pooled analysis in patients with low baseline HCV viral load (<400,000 IU/mL) SVR rates

were not statistically different between the 24- and 48-week treatment groups.^{277,278} The results support the conclusion, patients with genotype 1 who achieve a RVR and low baseline viral load (<400,000 IU/mL) may have their duration of therapy shortened to 24 weeks if there are no negative predictors of response, such as advanced liver fibrosis, cirrhosis, obesity, or insulin resistance.²³⁰ Meanwhile, in patients with genotype 4 with a RVR, the 24-week treatment group had a similar SVR rate to that of the 48-week treatment group, regardless of baseline viral load.^{275,279}

Treatment should be stopped in patients who do not achieve an EVR, as a SVR rate in these patients with standard treatment duration is <3%, and in patients with pEVR and detectable HCV RNA at week 24, as a SVR rate is 2-4%.^{235,236,280} Meanwhile, an additional 10-20% increase in SVR rate was reported in an extended treatment to 72 weeks when patients achieved a pEVR with negative HCV RNA at week 24.^{238,239,278,281} However, extension of duration of treatment should be carefully determined after considering many aspects of patients, such as adverse effects or compliance. In case of a cEVR without RVR, SVR rate was reported as 62-70%,^{230,237,239,275} and extension of the treatment duration did not increase the SVR rate.^{238,278}

Retreatment of HCV genotype 1 and 4 patients who fail to respond to previous treatment

Patients who have failed prior treatment can be classified as relapsers and non-responders. Retreatment with peginterferon alpha and ribavirin can be considered for relapsers who have previously been treated with conventional interferon alpha with or without ribavirin, or peginterferon alpha monotherapy, since SVR rates are reported as 31-47%.^{282,283} However, as for relapsers after peginterferon alpha and ribavirin therapy, a SVR rate after re-treatment with the same regimen was reported as only 23%, and retreatment should be carefully determined after discussion with the patient.²⁸⁴

In non-responders to conventional interferon alpha with or without ribavirin, retreatment with peginterferon alpha and ribavirin should be carefully determined considering that the SVR rate is very low (8-24%) in these patients.²⁸²⁻²⁸⁶ Retreatment with same regimen in non-responders to peginterferon alpha and ribavirin is not recommended, since SVR rates are only 4-8%. The retreatment should be postponed until DAAs are available.

During retreatment, SVR rates of patients with a cEVR is 35.1-49%, with a pEVR is 3.5-12%, and those without an EVR is

0-1%. Therefore, cEVR can be a useful marker in determining cessation of the retreatment.^{284,287,288}

A maintenance therapy with a low dose of peginterferon alpha is not recommended because it cannot reduce long-term complications in patients with advanced liver fibrosis or cirrhosis.^{285,289}

New therapies including DAAs in genotypes 1 and 4

Triple therapy including boceprevir or telaprevir

The standard therapy in Europe and the US during 2011-2013 was a triple therapy combining peginterferon alpha, ribavirin, and oral protease inhibitor, such as boceprevir or telaprevir. However, these two protease inhibitors have not yet been approved in South Korea.

In two phase III clinical trials using boceprevir^{257,290} and three phase III clinical trials using telaprevir,^{258,259,291} SVR rates were reported as 63-75%, 69-88%, and 29-33% in treatment-naïve patients, relapsers, and non-responders to peginterferon alpha and ribavirin, respectively. There were additional improvement in SVR by 25-30% in naïve patients and 25-60% in treatment experienced patients compared to combination therapy with peginterferon alpha and ribavirin.

However, more adverse effects were reported in triple therapy including boceprevir or telaprevir compared to the dual combination therapy.^{257,259,290,291} In the boceprevir trials, dysgeusia, anemia, and neutropenia were more common, while in the telaprevir trials, rashes, anemia, and anorectal symptoms (discomfort and pruritus) were more common. In addition, drug resistance should be considered because of the reduced drug compliance due to the discomfort and inconvenience in taking numerous drugs three times a day. Drug-drug interaction should also be considered, since boceprevir and telaprevir are metabolized in cytochrome P450 system (CYP2C, CYP3A4, and CYP1A) causing interaction with many other drugs. Information of drug interactions is provided in various websites (e.g., [www/hep-druginteractions.org](http://www.hep-druginteractions.org)). Another issue of increasing concern is differentiating patients who require immediate treatment with the triple therapy from those who can wait until drugs with improved adverse effects or lower prices are available, because the triple therapy imposes considerable expense.

Present situation for other newly developed drugs

Peginterferon lambda acts on receptors that are different from those of peginterferon alpha. The receptors of interferon lambda

are found mainly on hepatocytes. A clinical trial reported a higher RVR rate and significantly lower occurrence of adverse effects including hematologic side effects, flu-like symptoms, and muscular pain compared to peginterferon alpha.²⁹² New DAAs being evaluated in clinical trials include NS3/4A protease inhibitors (asunaprevir, faldaprevir, ABT-450, etc.), NS5A polymerase inhibitors (daclatasvir, etc.), NS5B polymerase inhibitors (sofosbuvir, deleobuvir, ABT-333, etc.), and host-acting antiviral agents include cyclophilin A inhibitor, miR-122 inhibitor (miravirsen).^{221,260-263,293-295}

These drugs can be simply administrated orally (except miravirsen, which is injected) with fewer adverse effects and stronger antiviral effects. A SVR12 rate (SVR rate at 12 weeks after the cessation of treatment) was 90% in a phase III clinical trial with sofosbuvir plus peginterferon alpha and ribavirin in 327 treatment naïve patients with chronic HCV (including 17% of cirrhosis patients) genotype 1, 4, 5, and 6 (seven patients of type 5 and 6).²⁶³

Many clinical trials with interferon-free, DAA combination regimens have been done or are ongoing. These have reported different therapeutic outcomes depending on the combination of drugs and subtypes (1a vs. 1b) of HCV.^{261,262,293,295,296} Therefore, a therapeutic strategy with more effective combination regimen, less adverse effect, and reduced drug resistance is expected to become available.

[Recommendations]

22. Optimal treatment of genotypes 1 and 4 (Fig. 2)

- 1) **Treatment with one of two peginterferon alpha molecules in combination with ribavirin should be planned for 48 weeks (A1). Peginterferon alpha-2a should be injected 180 µg subcutaneous once a week, regardless of patient body weight with ribavirin using doses of 1,000 mg/d for those ≤75 kg in weight and 1,200 mg/day for those > 75 kg. Peginterferon alpha-2b is to be injected at 1.5 µg/kg/week with ribavirin using doses of 800 mg for those <65 kg in weight, 1,000 mg for 65-85 kg, 1,200 mg for 85-105 kg, and 1,400 mg for >105 kg (A1).**
- 2) **In patients with a RVR and low baseline HCV viral load (<400,000 IU/mL), and without any negative predictors for SVR (advanced liver fibrosis, cirrhosis, obesity or insulin resistance), shortening of treatment duration to 24 weeks can be considered (B1).**
- 3) **In patients of genotype 4 with a RVR, 24-week**

treatment can be considered, regardless of baseline viral load (B2).

- 4) Treatment should be stopped in patients who fail to achieve an EVR (A1). Patients who achieve a cEVR can be treated for 48 weeks (A1). Patients with a pEVR should be re-tested at week 24; if HCV RNA remains positive, treatment should be stopped (A1), while if HCV RNA test becomes negative, extending therapy to 72 weeks can be considered (B2).**

23. Retreatment of HCV genotypes 1 and 4 patients who failed to respond to previous treatment

- 1) Retreatment with peginterferon alpha plus ribavirin can be considered for relapsers or non-responders that were previously treated with conventional interferon with or without ribavirin, or peginterferon monotherapy (B2). Patients who failed to achieve a SVR after peginterferon alpha and ribavirin combination therapy are not recommended to be retreated by the same regimen (A2).**
- 2) A low-dose maintenance therapy with peginterferon alpha is not recommended for patients who have failed a combination therapy with peginterferon alpha and ribavirin (A1).**

Triple therapy with peginterferon alpha and ribavirin plus either boceprevir or telaprevir is recommended for treatment naïve or experienced HCV genotype 1 patients (A1). It is desirable that more effective regimens including DAAs are adapted to Korean patients after further studies.

TREATMENT OF GENOTYPES 2 AND 3 CHRONIC HEPATITIS C

Optimal treatment of genotypes 2 and 3

The first-line treatment of HCV genotypes 2 and 3 patients is combination therapy of any one of two peginterferon alpha and ribavirin for 24 weeks.^{235,241,242,297-299} Peginterferon alpha-2a should be injected 180 µg subcutaneously once a week, regardless of body weight, whereas peginterferon alpha-2b is to be injected 1.5 µg/kg subcutaneously once a week. Ribavirin is to be given at a flat dose of 800 mg daily, regardless of the type of peginterferon

alpha used. There is insufficient evidence to show whether a weight-based dose of ribavirin is more effective in achieving a SVR for HCV genotype 2 and 3 patients.^{241,242,297} The SVR rate of Korean patients with HCV genotype 2 treated with the first-line therapy exceeded 80%.^{245, 300} Although a SVR rate of HCV genotype 3 in Korean patients is hardly been reported, reports from other ethnicities show a lower SVR rate in HCV genotype 3 patients by 10-20% than that of genotype 2.^{235,242,246,278,297,299,301-303}

Response-guided therapy in genotype 2 and 3 patients

Although several studies investigated whether the treatment duration could be shortened according to the on-treatment virological response,^{246,301-307} the results of these studies should not be compared directly since factors affecting SVR rates, such as duration of the shorted treatment, dose of ribavirin, proportion of patients with a RVR, are heterogeneous. A study comparing 16-week therapy with 24-week therapy each including about 350 patients reported a lower SVR rate of 65% in the 16-week treatment group compared to 82% in the 24-week treatment group.³⁰³ However, shortening of the treatment duration was not performed according to the on-treatment response, RVR, but was randomly assigned in this study. Meanwhile, in HCV genotype 3 patients, the same study reported a SVR rate of 61% in the 16-week treatment group and 71% in the 24-week treatment group that was not statistically significantly different. Another study compared 16-week and 24-week treatment groups of 200 HCV genotype 2 patients for each group, and reported a SVR rate of 81% in the 16-week group and 92% in the 24-week group, with no statistically significant difference.³⁰⁵ However, the 16-week treatment group had a relapse rate of 17%, which was significantly higher than that of the 5% rate of the 24-week treatment group. In addition, this study used weight-based dose of ribavirin from 1,000 to 1,200 mg in combination with peginterferon alpha and resulted in a higher relapse rate, despite an equivalent SVR rate, as that of the 24-week therapy. As for the factors predicting relapse after treatment other than the duration of the therapy, existence of cirrhosis, baseline high viral load, body weight, gender, and old age have been suggested.^{246,305,306} However, studies contradicting these results also exist, and further evidences are required.^{301,303}

In conclusion, patients with genotype 2 and 3 who achieve RVR may have their duration of therapy shortened to 16 weeks if there are no negative predictors of response, such as advanced liver

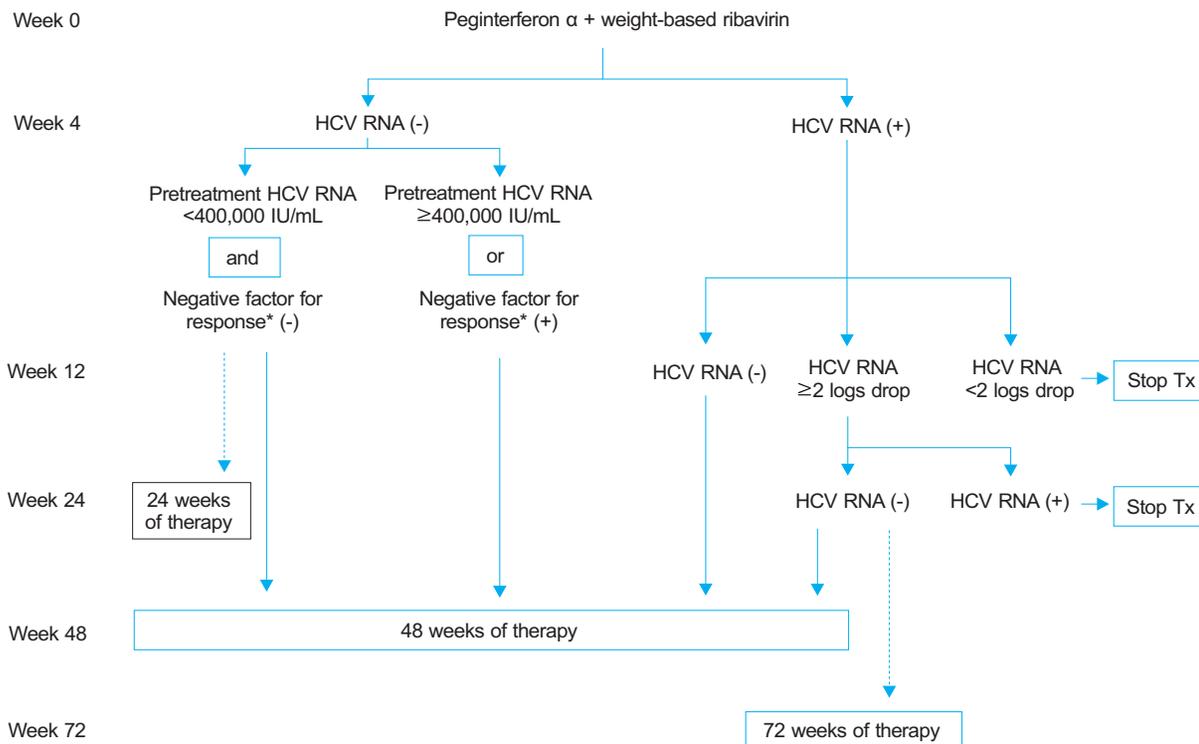


Figure 2. Treatment algorithm for patients with genotype 1 chronic HCV infection. This algorithm applies to genotype 4 at a B2 grade of evidence. The dotted lines indicated weaker strength of recommendation compared with the solid lines.

*Negative factors for response include advanced liver fibrosis or cirrhosis, obesity, and insulin resistance.

fibrosis, cirrhosis, and high baseline viral load, at the expense of a higher chance of post-treatment relapse. If negative predictors of response exist, such as advanced liver fibrosis or cirrhosis, there is a lack of evidence supporting equal efficacy of shortened therapy. Meanwhile, studies testing the efficacy of extended duration of treatment up to 48 weeks in patients with negative predictors for response, such as lack of RVR, high baseline HCV RNA level, or accompanying advanced liver fibrosis or cirrhosis. A study on 1,311 HCV genotype 2 or 3 patients with negative predictors for SVR reported no benefit of extended treatment duration to 48 weeks on achieving SVR.²⁴²

Retreatment of HCV genotype 2 and 3 patients who fail to respond to previous treatment

Retreatment with peginterferon alpha and ribavirin combination therapy may be given to HCV genotype 2 or 3 patients that were previously treated with conventional interferon with or without ribavirin, or peginterferon alpha without ribavirin, and failed to achieve SVR.^{282-286,308-310} The SVR rate after retreatment with peginterferon alpha and ribavirin combination therapy in relapsers

is reported to be 54.8-67.0%, whereas the SVR rate of non-responders after retreatment is 39.3-53.0%.^{282,283} There is insufficient evidence for adequate duration of retreatment in HCV genotype 2 and 3 patients, and previous studies on retreatment arbitrarily applied treatment duration of either 24 weeks or 48 weeks.^{282-285,308,310} A study including relapsers after 24-week of peginterferon alpha and ribavirin therapy who were retreated with the same regimen for the extended period of 48 weeks (n=92) reported a SVR rate of 57%.²⁸⁴ Therefore, for those who fail to achieve a SVR after peginterferon alpha and ribavirin treatment, there is still not enough evidence for the retreatment using the same regimen and it is not recommended, especially in non-responders.

New therapies in genotypes 2 and 3

Although a relatively high SVR rate can be achieved by 24-week combination therapy with peginterferon alpha and ribavirin in HCV genotype 2 and 3 patients, new therapeutic strategies may be required for patients that fail to achieve a SVR, and those who cannot tolerate interferon-based treatment. A phase III clinical trial investigating the efficacy of 12-week treatment of ribavirin

and sofosbuvir combination therapy on 70 treatment naïve HCV genotype 2 or 3 patients reported a SVR12 rate of 97%.²⁶³ In addition, a SVR12 rate of 94% was achieved after 16 weeks of sofosbuvir and ribavirin combination therapy in 32 treatment experienced chronic HCV genotype 2 patients.³¹¹ Therefore, interferon-free DAA combination regimens are effective in both treatment failure and interferon intolerant patients, and are expected to become available in Korea.

[Recommendations]

24. Optimal treatment of genotypes 2 and 3 (Fig. 3)

- 1) Treatment with one of two peginterferon alpha molecules in combination with ribavirin should be planned for 24 weeks (A1).
- 2) The dose for peginterferon alpha-2a is 180 µg subcutaneously once a week and peginterferon alpha-2b is 1.5 µg/kg per week (A1). Daily administration of 800 mg of ribavirin should be done, regardless of body weight (A2).
- 3) In patients with an RVR and without any negative predictors for SVR, shortening of treatment duration to 16 weeks can be considered (B2). However, shortening of treatment duration should be done in caution, since this can result in higher relapse rate (A2).

25. Retreatment of HCV genotype 2 and 3 patients who fail to respond to previous treatment.

- 1) Retreatment with peginterferon alpha plus ribavirin can be considered for relapsers or non-responders that were previously treated with conventional interferon with or without ribavirin, or peginterferon alpha monotherapy (B2).
- 2) Non-responders to a full course of treatment with peginterferon alpha plus ribavirin are not recommended to be retreated by the same regimen (B2).

TREATMENT OF GENOTYPE 6 CHRONIC HEPATITIS C

HCV genotype 6 is limited mostly to Southeast Asia, Southern China, Hong Kong, and Macau. It comprises about 1% of total chronic HCV patients in South Korea.³¹² SVR rate of chronic HCV genotype 6 treated with combination of peginterferon alpha and

ribavirin is 70.0-85.7%, which is comparable with that of HCV genotype 3 and higher than that of HCV genotype 1.³¹³⁻³¹⁵

A study comparing the efficacy of fixed dose ribavirin and weight based ribavirin for HCV genotype 6 patients is not available. All studies of peginterferon alpha based treatment for HCV genotype 6 have adapted weight based doses of ribavirin.³¹⁴⁻³²⁰

Two randomized control studies on combination therapy of peginterferon alpha and ribavirin reported no statistical difference in SVR between 24-week and 48-week treatment.^{72,80,318,320-323} No study has been conducted about retreatment for HCV genotype 6 patients who failed previous treatment.

[Recommendations]

26. Optimal treatment of genotype 6

- 1) Treatment with one of two peginterferon alpha molecules in combination with ribavirin should be planned for 24 weeks (A1).
- 2) The dose for peginterferon alpha-2a is 180 µg subcutaneously once a week and for peginterferon alpha-2b is 1.5 µg/kg per week (A1). Ribavirin is to be orally administered 1,000 mg in patients under 75 kg, and 1,200 mg in patients over 75 kg when administered with peg-interferon alpha-2a and 800 mg for under 65kg, 1,000 mg for between 65-85 kg, 1,200 mg for between 85-105 kg, and 1,400 mg for over 105 kg when given with peginterferon alpha-2b (B2).

TREATMENT OF ACUTE HEPATITIS C

Spontaneous recovery rate of acute hepatitis C varies from 20-50%.^{72,80,321-323} Treatment can be initiated immediately after the diagnosis of acute hepatitis C. However, evidence supports a therapeutic strategy of delaying treatment for 8-12 weeks to allow spontaneous remission.^{72,324,325} According to a randomized control study comparing an immediate treatment with a delayed treatment for 12 weeks, the SVR rate of the delayed treatment is not inferior to the immediate treatment considering spontaneous recovery rate and treatment-induced SVR.³²⁶ Nevertheless, diagnosis of acute hepatitis C is not always straightforward and treatment can be done in accordance with the treatment of chronic HCV infection when the differentiation of acute hepatitis

C and acute exacerbation of chronic hepatitis is difficult.

Anti-HCV antibody starts to appear at the time of highest ALT and of decreasing point of blood HCV RNA, which is about 8-12 weeks after the infection when most patients may not show any specific symptoms.¹³⁰ Therefore, testing for serum HCV RNA is useful for diagnosis and treatment when acute hepatitis C is suspected but showing a negative result for anti-HCV.

SVR rate is as high as 80-90% when acute hepatitis C is treated by conventional interferon alpha or by peginterferon alpha monotherapy for 24 weeks.³²⁷⁻³³³ Peginterferon alpha-2b and ribavirin combination therapy did not increase an SVR rate compared to that of peginterferon alpha-2b monotherapy.^{326,329} No clear additional benefits of combining ribavirin with interferon alpha or peg-interferon alpha are apparent to date.

The optimal treatment duration for acute hepatitis C is not definitely established. A randomized control study (n=34 in each group) reported no significant difference between SVR rates (82.4% in the 12-week treatment group and 91.2% in the 24-week treatment group) regardless of HCV genotypes.³³³ However, studies reporting good therapeutic outcomes of acute hepatitis C have tended to adopt a 24-week treatment, this length of treatment is recommended until contrary evidence is

presented.^{327,328,332,333}

[Recommendations]

27. Antiviral therapy is to be considered for treatment of acute hepatitis C (A1).

28. Initiation of treatment can be postponed for 8-12 weeks after onset of acute hepatitis C to allow spontaneous recovery (B2).

29. Peginterferon alpha monotherapy is preferentially considered in treatment of acute hepatitis C (B1), and duration of treatment is to be 24 weeks (B2).

MANAGEMENT OF ADVERSE EFFECTS OF ANTIVIRAL TREATMENT FOR HEPATITIS C

Monitoring adverse effects of antiviral treatment

During combination therapy of peginterferon alpha and ribavirin, many patients experience adverse effects; 10-20% of

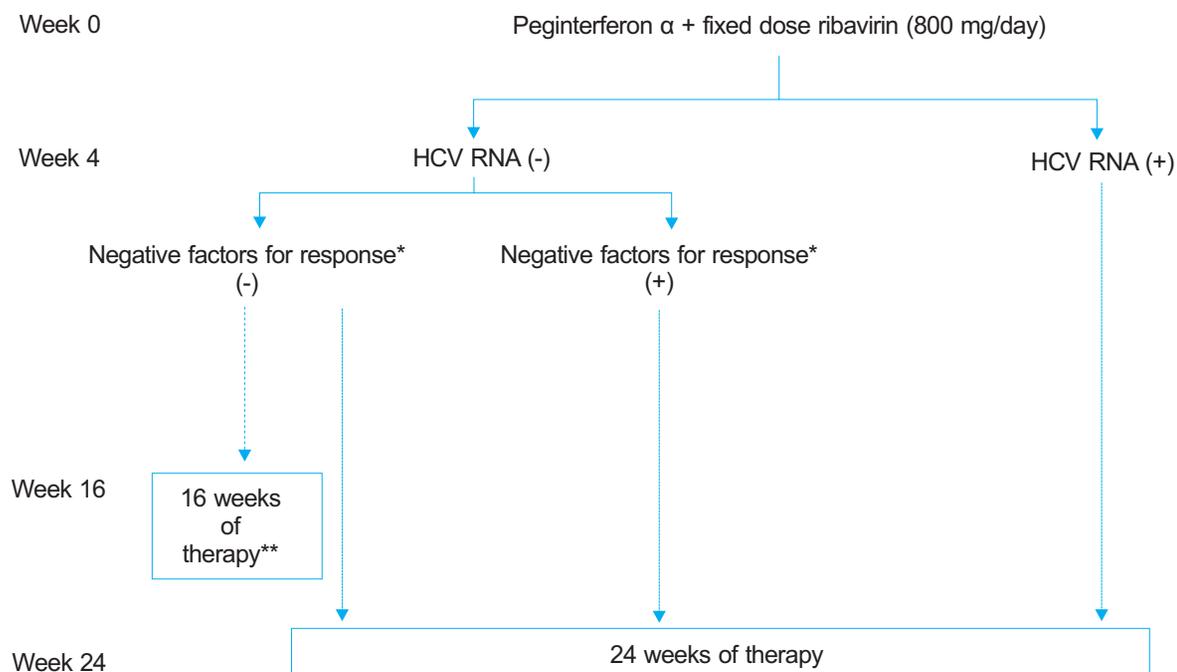


Figure 3. Treatment algorithm for patients with genotype 2, 3 chronic HCV infection. The dotted lines indicate weaker strength of recommendation compared with the solid lines.

*Negative factors for response may include advanced fibrosis, cirrhosis and others.

**The shortened therapy may result in higher relapse rate.

patients discontinue the treatment and 20-30% of patients experience dose reduction.^{334,335} Patients who received $\geq 80\%$ of both their planned peginterferon alpha and ribavirin doses for $\geq 80\%$ of the expected duration show an SVR rate of 63%, which was significantly higher than that (52%) of the patients who received reduced dose ($<80\%$) of one or both drugs.²⁵⁵ Therefore, meticulous monitoring and management of adverse effects can improve therapeutic outcome by preventing from drug discontinuation or dose reduction.

Adverse effects of antiviral therapy and its management

More than 20% of patients treated with the peginterferon alpha and ribavirin combination therapy experience headache, fever, myalgia, muscular rigidity, arthralgia, nausea, anorexia, weight loss, diarrhea, hair loss, skin rash, pruritus, inflammation on sites of injection, dyspnea, fatigue, insomnia, irritability, or depression (Table 9).^{235,241,242,336} However, severity or frequency of these adverse effects may vary, since these adverse reactions have been reported from patients chosen for clinical trials.³³⁶

Adverse effects after peginterferon alpha injection can be classified as flu-like symptoms, myelosuppression, neuropsychological problems, and autoimmune dysfunction. Flu-like symptoms including fever, fatigue, myalgia, or nausea occur in about 37% of the patients,^{235,241,242} but these symptoms can be alleviated by administration of analgesics and usually lessened 4-6 weeks after the treatment.³³⁶ Myelosuppression causes neutropenia and thrombocytopenia, the main causes of dose reduction, and often set the therapeutic limit in cirrhosis. Dose of peginterferon alpha should be reduced or skipped in case of severe adverse effects. Especially, when absolute neutrophil count decreases to under $750/\text{mm}^3$ or platelet count decreases to $<50,000/\text{mm}^3$, dose reduction should be considered; when absolute neutrophil count decreases under $500/\text{mm}^3$ or platelet count decreases under $25,000/\text{mm}^3$, drug discontinuation should be considered. Later, re-administration of the drugs can be considered following adequate recovery of absolute neutrophil count and platelet count; for example, 50% of the previous dose can be administered when absolute neutrophil count recovers up to $1,000/\text{mm}^3$ or over, and platelet count up to $75,000/\text{mm}^3$ or over, with continuous monitoring of those cell counts. Although evidences for the role of granulocyte colony stimulating factor (G-CSF) on lowering infection rate and on improving SVR are not enough, use of G-CSF can be considered in some patients with cirrhosis.³³⁷ Meanwhile,

treatment is to be halted in case of acute deterioration of hepatitis with elevation of ALT to over 10 times of upper-normal level or severe bacterial infection, such as sepsis. Even though thrombopoietin receptor agonist can raise platelet count in cirrhosis prior to treatment,³³⁸ use of this drug should be done very carefully, since evidence for improved SVR rate by this drug remain insufficient, whereas the risk of thrombosis can cause portal vein thrombosis.³³⁹

Neuropsychological problems including insomnia, difficulty in concentrating, memory impairment, irritability, or apathy can be caused by peginterferon alpha. Especially, severe depression can provoke a suicide attempt, which requires careful observation during antiviral treatment.³⁴⁰ Past history of depression should be checked for, since presence of uncontrolled depression is a contraindication to the treatment. Depression occurs in about 28% of patients during the treatment,³⁴¹ and antidepressants like serotonin uptake inhibitors can be used to maintain the treatment.³⁴² Preventive administration of antidepressants can reduce occurrence of depression during the treatment but cannot increase SVR rate.³⁴¹⁻³⁴³

Thyroid complications can occur in about 15-20% of patients, due to immunomodulatory function of peginterferon alpha,^{336,344} which may be from autoimmune or non-autoimmune causes; autoimmune thyroid diseases are classified as Graves' disease, Hashimoto's disease, and auto-antibody generation against thyroid gland³⁴⁵ and non-autoimmune thyroid disease results from thyroid damage by HCV itself.³⁴⁴⁻³⁴⁶ Hashimoto's disease is the most common and starts with hyperthyroidism and may progress to hypothyroidism. Thyroid function may not be recovered even after the cessation of treatment.³⁴⁷⁻³⁴⁹ Discontinuation of treatment should be considered in case of severe hyperthyroidism during interferon administration, while treatment can be maintained with careful observation if hyperthyroidism is not severe.³⁵⁰ In case of hypothyroidism at the beginning, interferon therapy can be maintained by administering thyroxine.³⁴⁴ Meanwhile, thyroid gland dysfunction can occur even after the end of treatment³³⁶ and it is desirable to check thyroid stimulating hormone (TSH) and free thyroxine levels at 2-4-month intervals during treatment and regularly for 1 year after the termination of treatment.

Various kinds of autoimmune diseases, such as systemic lupus erythematosus, type 1 diabetes mellitus, asthma, interstitial pulmonary fibrosis, or thyroid diseases, can be induced by interferon therapy.³⁵¹ Therefore, baseline evaluation of these diseases is necessary prior to the initiation of treatment, although existence of these diseases is not an absolute contraindication to the

Table 9. Adverse events of peginterferon alpha or interferon alpha and ribavirin

Possible related drug	Side effects
Peginterferon alpha or interferon alpha	Flu-like symptoms
	Fatigue
	Headache
	Fever
	Chill
	Myalgia
	Arthralgia
	Bone marrow suppression
	Neutropenia
	Thrombocytopenia
	Neuropsychiatric symptoms
	Depression
	Irritability
	Insomnia
	Apathy
	Autoimmune diseases
	Hashimoto thyroiditis
	Graves' disease
	Systemic lupus erythematosus
	Type 1 diabetes mellitus
	Bronchial asthma
	Pulmonary fibrosis
	Interstitial pneumonitis
Others	
Gastrointestinal	
Nausea	
Anorexia	
Dyspepsia	
Diarrhea	
Dermatologic	
Alopecia	
Rash	
Dry skin	
Skin itching	
Dry eye	
Dry mouth	
Stomatitis	
Psoriasis	
Reaction at injection site	
Ophthalmologic	
Vision impairment	
Retinal swelling	
Retinal hemorrhage	
Respiratory	
Cough	
Other	
Hearing loss	
Tinnitus	
Memory impairment	
Weight loss	
Ribavirin	
Hemolytic anemia	
Fatigue	
Rash	
Skin itching	
Teratogenic effect	

treatment especially when these diseases are well controlled.^{336,344} Other adverse effects related to peginterferon alpha, such as visual field defect, retinal hemorrhage and edema, hearing defect, tinnitus, vomiting, nausea, pruritus, weight loss or hair loss, improve after termination of treatment.³³⁶ Frequency of retinal defect is reported as about 3.8-30.9%³⁵²⁻³⁵⁶ with variable clinical course from severe visual field defect to no symptoms, and it is desirable to check the retina prior to the treatment in cases with risk factors such as old age, hypertension, or diabetes³⁵⁶⁻³⁵⁸ even though pretreatment and regular follow-up evaluation of retina remains debatable. Hearing loss occurs in <1% of patients and it cannot be recovered completely even after the termination of treatment.³⁵⁹

A common adverse effect of ribavirin is hemolytic anemia due to dose-dependent direct toxicity of ribavirin to erythrocytes and it may be a barrier to successful treatment.³⁶⁰ Anemia due to ribavirin can deteriorate ischemic heart or pulmonary diseases in patients with existing cardiac or pulmonary diseases.³⁶⁰ Immediate dose reduction by 200 mg should be considered when hemoglobin level decreases to under 10 g/dL and drug discontinuation should be considered in case of anemia with under 8.5 g/dL hemoglobin, but re-administration of the reduced dose is possible when anemia improves. Recombinant erythropoietin can be used in case of severe anemia, not to stop ribavirin or to prevent dose reduction, although the evidence of erythropoietin raising SVR rate is lacking.^{337,361} Meanwhile, it is apprehended that ribavirin causes congenital deformity during pregnancy, therefore thorough contraception is essential during treatment and for 6 months after treatment for both male and female patients.³⁶² Other adverse effects related to ribavirin include fatigue, pruritus, rashes, sinusitis, and gout.

Educating patients on treatment related adverse effects and their management helps to maintain the therapy. Detection of the adverse reactions during the first 2-4 weeks of the treatment is important and monitoring at 4-12 week intervals thereafter is required even if the patients seem to tolerate the antiviral therapy well.

[Recommendations]

30. A pretreatment evaluation of depression, cardiac and pulmonary diseases, hypertension, diabetes mellitus, thyroid diseases, or anemia is needed to monitor adverse effects of treatment (B1).

31. Monitoring of adverse effects at 2-4 week interval

after the initiation of the treatment and thereafter at 4-12 week intervals during the treatment (C1).

32. When absolute neutrophil count decreases to <750/mm³ or platelet count decreases to <50,000/mm³, dose reduction of peginterferon alpha should be considered; when absolute neutrophil count decreases to <500/mm³ or platelet count decreases to <25,000/mm³, discontinuation of peginterferon alpha should be considered. Later, re-administration of peginterferon alpha with reduced dose can be considered following adequate recovery of absolute neutrophil count and platelet count and continuous monitoring of those counts is needed (C2).

33. Dose reduction of ribavirin should be considered when anemia with hemoglobin level <10 g/dL occurs and discontinuation of ribavirin should be considered in case of hemoglobin level <8.5 g/dL. Later, when anemia improves, re-administration of ribavirin with reduced dose is possible and continuous monitoring of hemoglobin level is needed (C2).

34. Monitoring of TSH and free thyroxine levels at 2-4-month intervals is recommended to investigate the occurrence of thyroid abnormality (C1).

35. Appropriate management is needed when depression develops during the antiviral treatment and antiviral treatment should be halted in case of severe depression (C1).

MONITORING AFTER THE END OF TREATMENT

Continuous observation of undetectable HCV RNA after reaching SVR can be regarded as complete eradication of HCV. Re-infection of HCV is possible even after reaching SVR, mainly involving IVDU.³⁶³⁻³⁶⁶ Therefore, follow-up is needed to check re-infection or relapse of HCV after reaching SVR. A risk of HCC remained even after reaching SVR in case of accompanying cirrhosis or advanced hepatic fibrosis prior to the treatment.²¹⁴ In these patients, monitoring for HCC according to the surveillance strategy and management of general complications of cirrhosis are needed. If SVR is not achieved, the incidence of HCC and progress of the disease is significantly higher compared to the cases with SVR,^{214,367} and continuous management of chronic hepatitis is necessary in cases without SVR.

[Recommendations]

36. Continuous observation of undetectable HCV RNA after reaching SVR can be regarded as a complete eradication of HCV (C1).

37. A risk of hepatocellular carcinoma or complication of chronic liver disease still exist even after achieving SVR in patients with cirrhosis or advanced hepatic fibrosis, and continuous management and surveillance following the strategies for chronic liver disease are needed (B1).

38. If SVR is not achieved, continuous management of chronic liver disease is necessary (B1).

TREATMENT OF SPECIAL POPULATIONS

Considering that clinical trials on patients in specific medical conditions have many limitations, antiviral treatment in these populations should be individualized.

CIRRHOSIS

Treatment of patients with compensated cirrhosis

Compensated cirrhosis has a high probability of progression to decompensated cirrhosis or development of HCC. Thus, antiviral treatment is strongly recommended unless there are absolute contraindications. The acquisition of SVR in patients with cirrhosis or advanced hepatic fibrosis leads to the reduction of liver disease-related mortality and incidence of HCC.^{211,214,368,369} However, SVR rate of a combination therapy with peginterferon alpha plus ribavirin is significantly lower in patients with cirrhosis or advanced hepatic fibrosis compared to those patients with mild fibrosis. A Korean study reported SVR rates of 20.8% in genotype 1 HCV infected patients and 52.6% in genotype 2 HCV infected patients with Child-Turcotte-Pugh (CTP) class A cirrhosis.³⁷⁰ Also, meticulous monitoring and management of complications are necessary, since cirrhotic patients are usually elderly and treatment-related complications occur more frequently. Cirrhotic patients have low neutrophil and platelet counts due to portal hypertension and splenomegaly, so hematological problems including anemia, neutropenia, or thrombocytopenia often occur during treatment. Therefore, growth factors such as recombinant

erythropoietin or G-CSF could be helpful overcoming these complications.³⁷¹ Triple therapy using boceprevir or telaprevir has tended to produce a higher SVR rate than that of the standard combination therapy and a 48-week triple therapy resulted in higher SVR rate than that of 'response-guided therapy' in genotype 1 HCV-infected compensated cirrhotic patients.^{258,291,372} Therefore, the therapeutic efficacy of cirrhotic patients should be improved in the upcoming DAA era. Continuous monitoring for complications of cirrhosis is needed, even after reaching SVR, since there is still a possibility of development of HCC.

Treatment of patients with decompensated cirrhosis

Therapeutic outcome in decompensated cirrhotic patients is poorer with more frequent treatment-related complications compared to compensated cirrhosis. A small study (n=10, 8 genotype 1 HCV patients, 2 genotype non-1 HCV patients) reported a SVR rate of 20.0% in treating decompensated cirrhotic patients by a combination therapy with peginterferon alpha plus ribavirin.³⁷³ Therefore, antiviral treatment of CTP class B cirrhotic patients can be tried by experienced specialists with careful monitoring. Good therapeutic outcome is expected in case of low HCV RNA concentration, or HCV genotype 2 or 3. Although drug administration can be started with standard doses, more than half of the patients experience drug discontinuation or dose reduction. Thus, a careful approach starting with low accelerated dose regimen (starting with 90 µg/week of peginterferon alpha-2a or 0.5 µg/kg/week of peginterferon alpha-2b and 600 mg/day of ribavirin, and gradual increase of dose every 2 weeks up to the maximum tolerable dose)³⁷⁴ might be helpful.

The current standard treatment regimen is contraindicated in patients of CTP class C due to the likely possibility of severe complications including death.³⁷⁴ Efficacy and safety of DAAs have not been proven yet in treating decompensated cirrhosis.

[Recommendations]

39. Antiviral treatment is strongly recommended in CTP class A patients unless there are absolute contraindications, since HCV eradication decreases the risk of long-term complications, such as progression to decompensated cirrhosis or development of hepatocellular carcinoma (A1).

40. Meticulous monitoring and management of

treatment-related complications are necessary, since cirrhotic patients often have hematological problems due to portal hypertension and splenomegaly (A2). Growth factors can be helpful to overcome these complications (C2).

41. Continuous monitoring for appearance of cirrhosis-related complications and HCC is needed even after reaching SVR in cirrhotic patients (B1).

42. Antiviral treatment of CTP class B cirrhotic patients can be tried by experienced specialists with careful and meticulous monitoring (C2). Treatment can be started with standard doses or low doses of peginterferon alpha and ribavirin (C2).

43. The current standard treatment regimen is contraindicated in patients of CTP class C due to the likely possibility of severe complications including death (C1).

LIVER TRANSPLANTATION AND OTHER ORGAN TRANSPLANTS

Treatment following liver transplantation

Patients with HCV infection at the time of liver transplantation have higher graft failure rate (hazard ratio (HR), 1.30; 95% CI, 1.21-1.39) and mortality rate (HR, 1.23; 95% CI, 1.12-1.35) compared to patients without HCV infection.³⁷⁵ HCV reinfection occurs within several hours after transplantation in most of patients with detectable HCV RNA at the time of the transplantation.³⁷⁶ HCV-related liver diseases rapidly deteriorate following liver transplantation and around one-third of the patients progress to cirrhosis within 5 years after transplantation.^{375,377} Successful elimination of HCV after transplantation improves survival rate of the graft and patients.³⁷⁸

Treatment of HCV reinfection is recommended after histological confirmation of chronic hepatitis C at least 6 months after transplantation. The reason for this 6-month interval is that shortly after transplantation patients are heavily immunosuppressed and incompletely recovered from the surgery, resulting in high probability of drug intolerance as well as allograft rejection during interferon use. Antiviral treatment should be started as soon as possible when advanced fibrosis (numerous septa without cirrhosis) or portal hypertension is noted, since these conditions predict a rapid progression of liver diseases and graft failure.^{379,380} In case of fibrosis limited to the portal tract without portal hyper-

tension, antiviral treatment should be determined in consideration of treatment efficacy and risk of treatment-related complications.

The SVR rate of antiviral treatment after transplantation is 30-40%, and genotype 2 or 3 has better therapeutic outcome compared to genotype 1.^{378,381,382} Post-transplant patients reportedly show similar therapeutic outcomes (33% and 38% of SVR rates in each therapy) using either peginterferon alpha plus ribavirin combination therapy or peginterferon alpha monotherapy, which may be explained by frequent dose reduction or discontinuation of ribavirin due to complications.³⁸³ Anemia is the most common cause of treatment discontinuation and recombinant erythropoietin is recommended in this case.^{381,382} Allograft rejection can occur related to interferon alpha use, and liver biopsy is required to differentiate the cause of liver function deterioration during antiviral treatment. The on-treatment virological response of triple therapy using boceprevir or telaprevir in patients with recurrent chronic hepatitis C after liver transplantation is reported to be 50-60% at week 24 of treatment.³⁸⁴

Treatment following other organ transplants

Patients of renal transplant with HCV infection display rapidly progressing hepatic fibrosis and show high mortality related to hepatic failure. Thus, the presence of cirrhosis must be screened for prior to kidney transplantation.³⁸⁵ Sometimes liver biopsy is necessary to confirm cirrhosis. As hemorrhagic tendency exists in patients with end stage kidney disease (ESKD) due to platelet dysfunction, there is a concern that liver biopsy may cause procedure-related hemorrhagic complications. However, severe complications related to percutaneous liver biopsy have been rarely reported in patients with ESKD and the incidence of complications was not significantly higher than that of patients with normal renal function.³⁸⁶ Administration of 0.3 µg/kg desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP) can be used prior to liver biopsy when hemorrhagic complications are concerned.³⁸⁷

The combination therapy with peginterferon alpha plus ribavirin causes graft rejection in over 30% of patients, leading to graft failure and death. Thus, use of interferon-including regimen is an absolute contraindication in renal transplant patients except life-threatening fibrosing cholestatic hepatitis. Fundamentally, treatment of HCV is recommended prior to renal transplantation.³⁸⁸

There have been two successful cases of anti-HCV treatment using interferon in heart transplant setting.³⁸⁹ However, treatment

of HCV in heart transplant patients is not recommended except life-threatening fibrosing cholestatic hepatitis because of limited information. There are no available data on the situation of transplants of lung, pancreas, small intestine, or cornea.

[Recommendations]

44. Treatment of HCV reinfection after liver transplantation is recommended with histological confirmation of chronic hepatitis C (B1). Antiviral treatment should be started as soon as possible when advanced fibrosis or portal hypertension is noted, since these conditions predict a rapid progression of liver diseases and graft failure (B2). Treatment regimen could be either combination therapy with peginterferon alpha plus ribavirin or monotherapy with peginterferon alpha (B2).

45. Liver biopsy is often required to differentiate causes of liver function deterioration during antiviral treatment (C1).

46. Use of interferon based regimen is absolutely contraindicated in kidney, heart, and lung transplants except in life-threatening fibrosing cholestatic hepatitis (C1).

PATIENTS RECEIVING IMMUNOSUPPRESSANTS OR CYTOTOXIC CHEMOTHERAPY

There is no universal consensus on definition of HCV reactivation, although the commonly used criteria include blood level of ALT and HCV RNA. One study defined HCV reactivation as reemergence or increase of HCV RNA plus elevation of ALT up to 3 times of the upper normal limit.³⁹⁰

The incidence of HCV reactivation in patients taking immunosuppressants or under cytotoxic chemotherapy is lower compared to that of HBV.³⁹⁰⁻³⁹⁴ For example, the reactivation rate of HCV was 0% (0 of 11) compared to 38% (3 of 8) of HBV in a study including 98 non-Hodgkin's lymphoma patients receiving chemotherapy.³⁹⁵ However, another study of B cell non-Hodgkin's lymphoma reported higher incidence (26.3% vs. 2.1%) of significantly elevated ALT in HCV infected patients compared to patients without HCV infection, indicating that HCV reactivation does occur and may cause clinically significant morbidity.³⁹⁶

Risk factors predicting HCV reactivation have not clearly identified. However reactivation has been reported to occur more frequently in patients with hematological malignancies.^{392,397} HCV

reactivation has also been reported in patients with solid cancer or stem cell transplantation.³⁹⁸⁻⁴⁰¹ Although death due to HCV reactivation has rarely been documented,⁴⁰² the mortality is similar to that of HBV once severe hepatitis occurs with HCV reactivation.⁴⁰³⁻⁴⁰⁵

Strategies to prevent HCV reactivation in these patients have not been established. Conservative therapy and discontinuation of offending drugs are currently recommended options. However, one should take into account hepatic morbidity from HCV reactivation and disadvantages from immunosuppressive drug discontinuation, and decisions should be individualized. Further studies are needed to explore how to prevent and treat HCV reactivation by using DAAs.

TREATMENT OF ACTIVE INTRAVENOUS DRUG USERS

Intravenous drug abuse is the main route of HCV transmission and the abusers show significantly higher HCV infection rate compared to those without a history of drug abuse.^{114,406} Anti-HCV positive rate of Korean intravenous drug users has been reported as 48.4-79.2%.^{22,24,407} Meanwhile, high HCV infection rate also has been reported in case of sharing cocaine inhalation tubes.²⁵

A meta-analysis including over 2,800 injection drug users showed SVR rates as 44.9% in HCV genotype 1 and 70.0% in HCV genotype 2 and 3 patients treated by combination therapy of peginterferon alpha and ribavirin.⁴⁰⁸

The standard therapy is recommended only to the patients with a history of drug abuse but not for those that are actively using illicit drugs. Active drug users often show low willingness for HCV treatment, diminished ability to adhere to the treatment or abide by precautions regarding contraception, and higher possibilities of re-infection due to reuse of IV drugs. Therefore, it is important to clearly evaluate willingness of each patients for antiviral treatment and suspension from abusing illicit drugs for 6-12 months is usually needed despite of weak evidence supporting it.¹²⁵ Multidisciplinary cooperative treatment among medical and psychiatric counseling services, and social support showed a significant decrease of treatment interruption rate⁴⁰⁸ and resulted in cost-effectiveness by inhibition of disease progression.⁴⁰⁹

[Recommendations]

47. Multidisciplinary cooperative treatment among

medical and psychiatric counseling services and social support by specialists about drug abuse and improvement of social environment can raise degree of compliance to treatment in intravenous drug users (B2).

TREATMENT OF PATIENTS WITH CHRONIC KIDNEY DISEASES

HCV infection rate is high in chronic kidney disease patients. Yet, anti-HCV screening may not be needed for these patients. Screening should be selectively conducted when HCV-related glomerulonephritis clinically presenting as hematuria, albuminuria, or cryoglobulinemia is suspected. However, anti-HCV should be tested for in patients taking maintenance dialysis for the first time or transferred from other dialysis units. In addition, when unexplained abnormal liver-related biochemical tests is found or HCV exposure is suspected, anti-HCV should be tested and HCV RNA assay is needed in case of continuous negative detection of anti-HCV antibody.³⁷⁸ HCV prevalence among the patients taking dialysis is reported variously ranging from 3-80% depending on location;⁴¹⁰ the prevalence rate in South Korea is reported as 5-15%.^{26,27} The optimal surveillance interval for HCV infection in anti-HCV negative patients in dialysis unit should be between 6-12 months, considering the HCV infection rate of the dialysis unit where the patients are taken care of. Dialysis patients infected with HCV show higher mortality rate and rapid progress to cirrhosis or hepatocellular carcinoma compared to non-dialysis patients.⁴¹¹⁻⁴¹³ Patients scheduled for kidney transplantation should receive an anti-HCV assay. Survival rate after the kidney transplantation tends to be low with a possibility of graft rejection when interferon therapy were to be initiated after the transplantation and also with a possibility of increased occurrence of diabetes and membranous nephritis.⁴¹⁴⁻⁴²⁰ Therefore, interferon based antiviral therapy is recommended when HCV infection is confirmed via HCV RNA assay before impending necessity of kidney transplantation.³⁷⁸

Indications of HCV treatment in chronic kidney disease patients are to be determined considering liver disease condition and therapeutic complications. However, dose adjustment is needed depending on severity of kidney disease, since the clearance of both peginterferon alpha and ribavirin are reduced according to the degree of impaired kidney function. Moreover, ribavirin should be carefully used in case of creatinine clearance under 50 mL/min since ribavirin can cause severe hemolytic anemia.⁴²¹

Patients with mild kidney disease (glomerular filtration rate (GFR) ≥ 60 mL/min) can be administered the same dose of the therapeutic drugs as patients without kidney disease. If the patient has severe kidney disease (GFR of 15-59 mL/min), 135 μ g of peginterferon alpha-2a or 1 μ g/kg of peginterferon alpha-2b along with 200-800 mg/day of ribavirin twice a day with gradual dose increase is recommended.²⁷⁸ Patients on dialysis can take either interferon alpha or peginterferon alpha although combination with ribavirin is not recommended. SVR rate was variable as 7-97% in a study conducted using the combination therapy of peginterferon alpha (135 μ g/week) and low-dose ribavirin (200 mg/day) in patients on dialysis, and most studies reported a high rate of treatment discontinuation.

Dose adjustment of new drugs, such as boceprevir and telaprevir, is not necessary since they are metabolized in the liver and eliminated mostly through feces and negligibly through urine.⁴²² However, SVR rates after the treatment with these drugs have not been reported yet in chronic kidney disease patients.

Antiviral therapy for HCV can be conducted in patients having HCV-related cryoglobulinemia or membranous glomerulonephritis. Immunosuppressive therapy or plasma exchange can be done prior to the antiviral treatment in case of nephrotic syndrome or rapid decrease of kidney function among these patients.⁴²³⁻⁴²⁵

[Recommendations]

48. Anti-HCV should be tested to plan further treatment and management in patients preparing kidney replacement therapy, such as dialysis or kidney transplantation (B1).

49. HCV RNA should be tested to confirm HCV infection in patients having idiopathic liver diseases despite of negative anti-HCV results or in patients with positive anti-HCV (B1).

50. Combination therapy of peginterferon alpha (135 μ g of alpha-2a or 1 μ g/kg alpha-2b) and ribavirin (200-800 mg/day) or therapy of interferon alpha and ribavirin can be used in chronic hepatitis C patients with severe kidney disease not undergoing hemodialysis (15-59 mL/min of glomerular filtration rate) (C2).

51. Treatment of HCV in patients on dialysis may be considered with either interferon alpha (2a or 2b, 3,000,000 units, three times a week), or reduced dose of peginterferon alpha (2a, 135 μ g/week or 2b, 1 μ g/kg/week) (C2).

TREATMENT OF PATIENTS WITH HIV OR HBV COINFECTION

Chronic hepatitis C patients with HIV coinfection

Coinfection rate of HIV and HCV is reported to be 25% in western countries²⁸ and 5.0-6.6% in South Korea.^{29,30,426} Since the frequency of coinfection is relatively high, all HIV infected patients should receive HCV testing consisting primarily of an anti-HCV assay. However, antibody formation may fail to appear in about 6% of HIV infected patients and a HCV RNA assay should be conducted in patients with idiopathic liver disease and negative anti-HCV.^{427,428} Chronic hepatitis C patients with risk factors of HIV infection should be tested for HIV.

HIV coinfecting patients show rapid progress of liver disease and 2-fold higher incidence rate of cirrhosis compared to HCV mono-infection. Therefore, liver diseases due to HCV is regarded as an important factor affecting morbidity and mortality rate in HIV infected patients, since highly active antiretroviral therapy (HAART) was introduced in 1996.⁴²⁹⁻⁴³¹ Especially, progression of liver disease speeds up as CD4+ lymphocyte count is lower and immune disorder is more severe.⁴³² Recovery of immune function by antiretroviral therapy can delay the progress of liver disease.⁴³³⁻⁴³⁵ Generally, antiretroviral therapy is recommended in HIV/HCV coinfecting patients regardless of CD4+ lymphocyte count, since the benefits from antiretroviral therapy are bigger than risk of drug toxicity. However, antiretroviral therapy should be conducted carefully due to high risk of liver toxicity, especially in HIV/HCV coinfecting patients with progressed liver disease.^{436,437} It is desirable to adapt antiretroviral therapy first when CD4+ lymphocyte count is low and to adapt HCV treatment after the recovery of CD4+ lymphocyte count. Meanwhile, antiretroviral therapy can be delayed in patients with a CD4+ lymphocyte count >500 cells/mm³.⁴³⁸

Peginterferon alpha can be used at same dose recommended for treating HCV mono-infection and ribavirin dose can be adjusted depending on body weight (1,000 mg/day for under 75 kg, 1,200 mg/day for over 75 kg),⁴³⁹ regardless of HCV genotype in HIV coinfection. Treatment duration is usually recommended as 48 weeks, regardless of HCV genotype. A shortened duration of therapy down to 24 weeks can be effective in genotype 2 and 3 with RVR, and an extended duration of therapy up to 60-72 weeks can be helpful in genotype 1 and 4 with pEVR and no RVR.^{114,439-443}

SVR rate of the combination therapy in HIV coinfection was reported as 29% in genotype 1 and 62% in genotype 2 and 3.⁴⁴⁴ Lower SVR rate compared to that of HCV mono-infection may be related to the high blood concentration of HCV RNA in HIV coinfecting patients compared to that of HCV mono-infection.⁴⁴⁴⁻⁴⁴⁸

Anemia related to ribavirin is a raising problem in treatment of HIV coinfection and especially it is more frequent and severe in patients taking zidovudine (AZT).⁴⁴⁹ Ribavirin can deteriorate didanosine (ddl) toxicity by inhibition of inosine-5-monophosphate dehydrogenase and severe lactic acidosis has been reported in patients taking ddl along with ribavirin.⁴⁵⁰⁻⁴⁵³ Therefore, patients receiving AZT and especially ddl should be switched to an equivalent antiretroviral agent before beginning combination therapy containing ribavirin.

SVR rate of triple therapy using boceprevir was 60.7%, which is superior to the 26.5% reported in the dual combination therapy, and triple therapy using telaprevir showed higher SVR rate (74%) compared to 45% in the combination therapy. Adverse effects of the triple therapy in HIV coinfection have been reported to be similar to those occurring in HCV mono-infection although further studies are needed.⁴⁵⁴ In addition, detailed monitoring is necessary when using the regimens including boceprevir or telaprevir due to possible drug-drug interactions.⁴²²

[Recommendations]

52. All HIV infected patients should take anti-HCV test (B1).

53. HCV RNA assay should be conducted in patients having idiopathic liver disease even with negative anti-HCV or in patients with positive anti-HCV (B1).

54. Peginterferon alpha should be used at same dose recommended for treating HCV mono-infection and ribavirin dose can be adjusted depending on body weight for 48 weeks regardless of HCV genotype in HIV co-infected patients (B1).

Chronic hepatitis C patients with HBV coinfection

The number of HBV/HCV coinfecting patients worldwide is estimated as 15,000,000,⁴⁵⁵ and 2.37% of the anti-HCV positive patients are reported to be coinfecting with HBV in South Korea.⁴⁵⁶ A 10-year follow-up study of HCV mono-infected patients reported HCC occurrence rate of 28%, whereas HCV/HBV coinfecting

patients showed a occurrence rate of 45%, which was significantly higher.⁴⁵⁷ In addition, risks of severe and fulminant hepatitis increase and the incidence rate of cirrhosis and HCC increases in case of HBV/HCV coinfecting patients compared to HBV monoinfection.⁴⁵⁸⁻⁴⁶⁰

In patients with HBV/HCV coinfection, blood levels of HCV RNA and HBV DNA representing replicative status of each virus should be evaluated, and if HCV infection is the dominant cause of the liver disease, the same antiviral therapy as for HCV monoinfection is recommended for an SVR rate, similar to that of HCV monoinfection.⁴⁶¹⁻⁴⁶³ Reactivation of HBV is possible during or after HCV treatment,⁴⁵⁶ and administration of oral antiviral agents may be indicated when significant proliferation of HBV is confirmed in this case.⁴⁶⁴

[Recommendation]

55. After confirming the dominant cause of liver diseases in HBV/HCV coinfection, treatment based on the standard therapy of HCV monoinfection is recommended and oral administration of anti-HBV agents may be indicated when significant proliferation of HBV is confirmed (B1).

TREATMENT OF PATIENTS WITH HEMOPHILIA OR THALASSEMIA

Accompanying HCV infection in patients with hemophilia or thalassemia causes significant increases of morbidity and mortality rates compared to patients without HCV infection.⁴⁵⁶⁻⁴⁶⁹ Therefore, aggressive treatment of HCV infection should be considered and the combination therapy of peginterferon alpha and ribavirin is recommended. Therapeutic outcomes in both HCV infected cases with or without hemophilia were similar and there was no increase in complications regarding bleeding tendency.⁴⁷⁰ Severe anemia can occur due to ribavirin in thalassemia and up to 30-40% of cases may require blood transfusion to maintain 9-10 g/dL of hemoglobin at 3-4 week intervals. Therefore careful monitoring is required to confirm hematological complications. However, discontinuation of treatment or incidence of other main complications did not increase in these patients.⁴⁶⁵

[Recommendation]

56. The combination therapy of peginterferon alpha and ribavirin is recommended in treating chronic hepatitis C patients accompanying hemophilia or thalassemia (B1).

TREATMENT OF CHILDREN WITH CHRONIC HEPATITIS C

A Korean study recruiting 2,080 children reported an anti-HCV positive rate of 0.82% in 1998.²⁰ Transfusion of infected blood components or vertical transmission is the most common cause of HCV infection in children,⁴⁷¹ although transfusion-related HCV transmission has been rarely reported after the introduction of screening test in 1991 in South Korea. The global HCV infection rate of pregnant women has been reported as 0.49-1.7%.¹⁵⁻¹⁷ Korean studies including 5,000 pregnant women and another study on 20,000 pregnant women showed anti-HCV positive rate of 0.42-0.44%, where 57-60% of anti-HCV positive pregnant woman resulted in HCV RNA positive.^{18,19} Transmission of HCV was reported as 1-6.2% during the perinatal period^{65,67,472,473} and the evidence of lowering the risk of vertical HCV transmission by Cesarean section is weak.⁴⁷⁴ An anti-HCV assay in children is recommended at over 18 months of age, since maternal antibodies can be delivered to newborns.⁴⁷⁴⁻⁴⁷⁶ HCV RNA assay may be performed at 1 or 2 months of age if an earlier diagnosis is desired, although the sensitivity of this assay is as low as 22% at that time; it is desirable to conduct the HCV RNA assay at the age over 6 months when the sensitivity reaches 85%.^{475,477}

Spontaneous recovery is more frequent in children having high tendency of a normal ALT level⁴⁷⁸ along with slow progress of hepatic fibrosis and, rarely, severe hepatic damage. However, aggressive treatment instead of waiting until the children grow has been suggested, since children usually have regular life cycle and show higher therapeutic compliance. Aggressive treatment is considered in case of continuously elevated serum AST/ALT or when progressed hepatic fibrosis is confirmed by liver biopsy. In addition, treatment can also be considered when serum AST/ALT is normal or fibrosis is mild by liver biopsy since evaluating tools of predicting disease progression are not sufficient in children.⁴⁷⁹

Although in the past studies on HCV infected children, treatment was limited to interferon alpha monotherapy due to the potential teratogenic effects of ribavirin, higher SVR rates have been reported with the addition of ribavirin to treatment

recently.⁴⁸⁰⁻⁴⁸⁴ Therefore, most studies have adapted the combination therapy in children, since this approach is standard in adults. Use of peginterferon alpha in children over 3 years of age was approved in North America and Europe.⁴⁷⁹ The dose of peginterferon is 60 µg/m²/week for alpha-2b and 180 µg/1.73m²/week for alpha-2a and the dose of ribavirin is 15 mg/kg twice a day. Genotype 1 and 4 patients should be treated for 48 weeks and genotype 2 and 3 patients should be treated for 24 weeks, similar to adults.⁴⁷⁹ SVR rate after the combination therapy of peginterferon alpha and ribavirin (47-53% in genotype 1 and 80-100% in genotypes 2 and 3) is superior to that of the combination therapy of interferon alpha and ribavirin.⁴⁸²⁻⁴⁸⁴ Factors predicting SVR include genotype 2 and 3, and HCV RNA titer <600,000 IU/mL.^{480,483,484} Efficacy and safety of boceprevir or telaprevir have not been proved yet in children <18 years of age.⁴²²

[Recommendations]

57. Diagnosis and evaluation of HCV in children should proceed following the similar steps as in adults (B1).

58. Anti-HCV assay in children is recommended at the age over 18 months since maternal antibodies can be delivered to newborns. If an earlier assay is required, HCV RNA assay may be considered after 6 months of age (B2).

59. HCV infected children aged 3-17 years should be considered as appropriate treatment candidates according to the same criteria used in adults (B1).

60. The dose of peginterferon alpha is 60 µg/1.73 m²/week for 2b and 180 µg/1.73 m²/week for 2a and the dose of ribavirin is 15 mg/kg/day. Genotype 1 and 4 patients should be treated for 48 weeks and genotype 2 and 3 patients should be treated for 24 weeks (B1).

Conflicts of Interest

The authors have no conflicts to disclose.

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