Update on Treatment of Chronic Hepatitis C

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INTRODUCTION

Since the release of Korean guidelines for chronic hepatitis C management in the mid of 2000s, two major advances have occurred: the development of direct-acting antiviral agents (DAAs) with dramatically improved rates of virological clearance compared with standard therapy [1-5] and the recognition of several single nucleotide polymorphisms (SNPs) associated with an increased probability of treatment-induced viral clearance [6,7].

Unlike Hepatitis B virus (HBV), Hepatitis C virus (HCV) replicates exclusively at the cytoplasm of liver cells without host genome integration [8]. Eradication of infected cells with blockage of further viral replication may lead to the cure of the infection. The standard of care (SOC) therapy for patients with chronic HCV infection has been the use of both PegIFN-α and ribavirin. PegIFN-α acts as a potent antiviral agent which inhibits virus production, and may also plays a role in removing the infected cells [9,10]. Ribavirin, when used with IFN-α, seems to accelerate the removal of HCV-infected cells through the mechanism not fully understood [11,12]. These drugs are administered for either 48 weeks (HCV genotypes 1, 4, 5, and 6) or for 24 weeks (HCV genotypes 2 and 3), inducing SVR rates of 40-55% in those with genotype 1 and of 80% or more in those with genotypes 2 and 3 infections [13-15]. As a matter of fact, undetectable HCV RNA, 24 weeks after completion of treatment, known as SVR, is considered as "the cure", leaving the chance of the HCV recurrence less the 1% [16].

Two PegIFN-α molecules can be used in combination with ribavirin, i.e. PegIFN-α2a and PegIFN-α2b. The pharmacokinetics of these compounds differs. A large-scale US trial comparing the efficacy of PegIFN-α2a and PegIFN-α2b with ribavirin in patients infected with HCV genotype 1 showed no significant difference[17]. In contrast, two Italian trials in patients infected with HCV genotypes 1, 2, 3, and 4 showed some benefit, mostly in genotype 1 patients, in favor of PegIFN-α2a in combination with ribavirin[18, 19]. Although efficacy is still debated, there is currently no conclusive evidence that one PegIFN-α2 should be preferred to the other one as first-line therapy.

In order to increase the SVR rate, efforts has been made to develop new therapeutic molecules active on HCV, direct-acting antivirals (DAAs), for this potentially curable infection.

PATIENTS FOR WHOM THERAPY IS WIDELY ACCEPTED

Therapy is generally accepted for patients with all of the following characteristics : at least 18 years of age, HCV RNA detectable in the serum, liver biopsy with chronic hepatitis and significant fibrosis (bridging fibrosis or higher), compensated liver disease, total serum bilirubin < 1.5 g/dL, Prothrombin time INR < 1.5, albumin > 3.4 g/dL, platelet count > 75,000 cells/mm^3, hemoglobin >13 g/dL for men and >12 g/dL for women, neutrophil count >1,500 cells/mm^3, creatinine <1.5 mg/dL, no evidence of hepatic encephalopathy or ascites. In addition, the guidelines do not currently recommend treatment in patients with decompensated liver disease, HBV co-infection, or active cancer, or in patients who have

undergone organ transplantation due to limited data.

EVALUATION PRIOR TO TREATMENT

Liver biopsy

Most patients undergo liver biopsy prior to treatment of chronic HCV infection, although the usefulness of routine biopsy continues to be debated. Generally a liver biopsy is undergone prior to treatment in patients with genotypes 1 and 4. For patients with genotypes 2 and 3 we do not routinely performed a pretreatment liver biopsy, but we recommend a liver biopsy in those who do not respond to therapy. Following treatment, we do not perform a repeat liver biopsy in patients who have had a SVR. By contrast, the follow-up liver biopsy may be performed with at least two years interval to evaluate disease progression in patients who do not respond to treatment or who decline treatment. There is little information on the appropriate interval for subsequent evaluations. Noninvasive measures of hepatic fibrosis may be an alternative to liver biopsy in selected patients.

Alcohol abstinence

Alcohol abuse reduces the responsiveness to interferon, accelerates disease progression, and increases the risk of hepatocellular carcinoma [20]. As a result, patients with chronic hepatitis C should be counseled not to drink alcohol. In addition, steatosis is associated with lower treatment response rates.

Other medical conditions affecting therapy

Prior to initiating antiviral therapy, a thorough evaluation for following conditions that might affect therapy should be investigated. Autoimmune disorders, active major depression may be at increased risk from therapy with interferon. Patients with concurrent human immunodeficiency virus (HIV) infection have an accelerated rate of progression of HCV. Patients who have insulin resistance have lower sustained virologic response rates.

MANAGING DIFFICULT–TO–TREAT SITUATIONS

While the decision to offer therapy to a treatment-naïve patient without any contraindications is usually straight-forward, the decision is more complicated in patients who do not meet eligible criteria.

Relapsers and nonresponders

The decision to retreat patients who fail to respond to treatment or who relapse after treatment should take into account the viral genotype and other predictive factors of response.

In addition, IL28B genotype (CC, CT, or TT) may be a factor to take into consideration. In patients who had failed prior therapy for HCV genotype 1, IL28B genotype CC was associated with an increased chance of attaining an SVR[21].

Persistently normal serum ALT

Up to 30 percent of patients with chronic HCV infection have a persistently normal serum ALT level. The optimal management of such patients remains controversial. A role for treatment is supported by the observation that some of these patients have substantial inflammation on liver biopsy [22]. In addition, the response to combination therapy with peginterferon plus ribavirin in patients with normal serum aminotransferases is similar to the response in those with elevated aminotransferase levels.

It is reasonable to withhold treatment in patients with persistently normal serum ALT levels who have characteristics associated with slower rates of progression of hepatic fibrosis, such as HCV acquisition before the age of 35 years, female sex, alcohol abstinence, and no or minimal fibrosis on liver biopsy [23]. By contrast, we offer treatment to patients who do not fit this profile and whose initial biopsies show moderate activity or some degree of fibrosis because the risk of disease progression is increased in such patients.

Mild liver disease

Patients who have a persistent elevation in serum ALT levels but do not have fibrosis and have minimal necroin-

flammatory changes are likely to have slow disease progression. Such patients can be monitored periodically. However, the decision to treat should be individualized.

Advanced hepatic fibrosis and compensated cirrhosis

Treatment strategy for compensated cirrhosis has been based on the subgroup analyses of large clinical trials. The response rate is lower in these patients than in those without cirrhosis and the use of growth factors (such as erythropoietin, granulocyte colony-stimulating factor, and granulocyte macrophage colony-stimulating factor) may be helpful during treatment by limiting the need for reductions in the dose of antiviral therapy.

Patients with chronic HCV and advanced fibrosis who did achieve an SVR had a much lower risk of liver-related mortality. Patients who attained an SVR were also significantly less likely to develop hepatocellular carcinoma or hepatic decompensation[24, 25]. Based upon the improved prognosis in patients with advanced fibrosis or compensated cirrhosis who receive treatment with peginterferon and ribavirin, we suggest that these patients receive treatment if there are no contraindication. In addition, patients with genotype 1 should receive telaprevir or boceprevir.

Decompensated cirrhosis

The primary treatment for patients with decompensated cirrhosis is liver transplantation. However, a few reports described treatment of decompensated cirrhotic patients with peginterferon and ribavirin has been associated with substantial side effects and dropouts, but experienced hepatologists may hope that antiviral therapy using IFN-free regimen will be available in the near future.

Recurrence after liver transplantation

Recurrence of HCV occurs in more than 95 percent of patients after liver transplantation. Disease progression in this setting is more rapid, and complications are more frequent than in immunocompetent patients with HCV infection [26]. Disease progression correlates with HCV RNA levels at the time of transplantation, the age of the organ donor, and the degree of immunosuppression in the post-transplant period. There are few high-quality studies to guide treatment of HCV after liver transplantation. Antiviral therapy is generally initiated only if there is significant histologic liver injury. However, the therapeutic options are limited in this population, and rigorous clinical trials are difficult to conduct.

Ongoing alcohol use

Alcohol is an important cofactor in HCV disease progression, and the amount of alcohol that is safe during treatment is unknown. Although a history of alcohol abuse is not an absolute contraindication to clinical therapy, continued alcohol use during therapy adversely affects response to HCV. Therefore, patients should be encouraged to abstain from alcohol.

DAAs: A NEW STANDARD OF CARE FOR HCV

Recent developments in understanding HCV replication made it possible to identify several potential targets for DAA drugs. Classes of molecules that belong to nonstructural protein 3/4A (NS3/4A) protease inhibitors, nucleoside/nucleotide analogue and non-nucleoside inhibitors of the HCV RNA-dependent RNA polymerase, and inhibitors of the HCV non-structural protein 5A (NS5A) are the ones that are designed to block viral replication. In addition, cyclophylin inhibitors are structured to block the host cell protein, cyclophylin, which is required to interact with the replication complex for efficient viral genome production [27].

Currently, two HCV treatment strategies are being evaluated: adding one or two DAAs to PegIFN and ribavirin (PegIFN/RBV), the current SOC; and giving an all-oral DAA combination designed to inhibit different steps of the HCV life cycle (an approach that has been successful at controlling, but not curing, HIV infection). Adding a hepatitis C protease inhibitor to SOC has greatly improved response rates in clinical trials. Triple therapy (DAA plus SOC) may also shorten treatment duration. Phase III clinical trials using NS3/4A

protease inhibitors showed significant increases in SVR rate as follows: 3 studies with Telaprevir are ADVANCE [2], ILLUMINATE [3], REALIZE [4] and 2 studies with Boceprevir are SPRINT-2 [1], RESPOND-2 [5]. Boceprevir and telaprevir have been approved by the Food and Drug Administration (FDA) of the Unites States for the treatment of genotype 1 HCV patients in 2011. Both DAAs are still the only ones that have been proved for their efficacy against treatment- naïve and previously treated genotype 1 HCV patients. Recently, AASLD and UK consensus guidelines were released regarding the treatment of genotype 1 patients with protease inhibitor based-triple therapy [28,29].

Treatment-naive individuals

For treatment-naive patients, the duration of therapy is determined by assessment of the HCV RNA level at specific time points, which vary between the two HCV protease inhibitors (ie, "response-guided therapy").

Boceprevir

The SPRINT-2 clinical trial demonstrated that adding boceprevir to standard therapy increased SVR rate from 38% (PegIFN/RBV) to more than 60% (boceprevir, PegIFN/RBV) in nonblack genotype 1 HCV patients that has never been treated before [1]. Treatment-naive patients should be treated with PegIFN/RBV for 4 weeks ("lead-in"), after which boceprevir 800 mg by mouth thrice daily is added for 24 weeks' duration. For most patients, the duration of total therapy is determined by the achievement of a rapid virologic response (RVR) defined as HCV RNA suppression to below detection by treatment week 8. Patients with suppression by treatment week 8 may be treated for 28 weeks, whereas those with detectable HCV RNA at treatment week 8 and suppression prior to treatment week 24 should be treated for 48 weeks, of which the final 12 weeks include only PegIFN/RBV. Since SPRINT-2 clinical study also demonstrated the lower SVR rate in patients with advanced fibrosis, it has been recommended by FDA that response-guided therapy should be reserved only for the patients without liver cirrhosis. Patients with compensated cirrhosis or poor interferon response during the lead-in phase should be treated for 48 weeks (4 weeks of PegIFN/RBV followed by 44 weeks of boceprevir triple therapy). The efficacy of boceprevir seems to be different according to race, ongoing clinical study over Korean population would provide more accurate perspective.

Telaprevir

Treatment-naive patients should be treated with PegIFN/RBV plus telaprevir 750 mg by mouth thrice daily for 12 weeks, after which telaprevir should be discontinued and PegIFN/RBV continued for an additional 12 or 36 weeks. This ADVANCE clinical trial showed that triple therapy using telaprevir resulted in higher SVR rate in HCV genotype 1 patients that were never been treated before, compared with SVR rate of patients that were treated with only PegIFN/RBV for 48 weeks (75% vs. 44%) [2]. Teleprevir was also effective in treating black patients as compared to the conventional therapy that uses only PegIFN/RBV (62% vs. 25%).

The ILLUMINATE trial which focused on respond-guided therapy showed that patients that achieved eRVR have the treatment shortened without jeopardizing the SVR rate [3]. Respond-guided therapy can also be applied when treating with telaprevir. Patients whose HCV RNA was undetectable at week 4 and 12, designated as having "extended RVR" (eRVR), and had the duration of therapy shortened to 24 weeks. Patients with detectable HCV RNA at treatment week 4 or at week 12 who achieve HCV RNA suppression to undetectable prior to treatment week 24 ("late" responders) should be treated for 48 weeks, of which the final 36 weeks include only PegIFN/RBV. Application of respond-guided therapy in cirrhotic patients might need some caution since cirrhosis itself has adverse effect on achieving SVR.

Treatment-experienced individuals

The regimens for treatment-experienced individuals are similar to those for treatment-naive individuals, but the duration of therapy is determined by time to an undetectable HCV RNA and/or by the prior treatment response to PegIFN/RBV.

Boceprevir

The patients who had received therapy for chronic hepatitis C without success can be categorized as the followings: null responders whose HCV RNA level did not decline by at least 2 log IU/mL at treatment week 12; partial responders whose HCV RNA level dropped by at least 2 log IU/mL but whose HCV RNA was still detectable at treatment week 24; relapsers whose HCV RNA became undetectable during treatment, but reappeared after treatment ended.

The RESPOND-2 clinical trial demonstrated that adding boceprevir to SOC increased SVR rate from 21% (PegIFN/RBV) to more than 59% (boceprevir, PegIFN/RBV) in genotype 1 HCV partial responders or relapsers[5]. The study design was very similar to that of SPRINT-2 clinical trial, and had three groups, after lead-in therapy. However, the group where response-guided therapy was performed had the duration of the therapy shortened to 36 weeks instead of 28 weeks. The relapsers achieved highest SVR rate (75%) when triple combination therapy (boceprevir, PegIFN/RBV) was performed for 44 weeks. In the group where response-guided therapy was given, SVR rate was slightly lower (69%) but it was not statistically significant.

Patients with prior viral relapse and partial response should be treated with response-guided therapy based on the treatment week 8 HCV RNA level (undetectable or detectable). Patients would receive boceprevir triple therapy ending at week 36 but PegIFN/RBV continuing through week 48 if detectable. Treatment-experienced patients with cirrhosis or prior null response should be treated for 48 weeks (4 weeks of PegIFN/RBV followed by 44 weeks of boceprevir triple therapy).

Telaprevir

In REALIZE clinical trial, adding telaprevir to PegIFN/RBV for 12 weeks with or without lead-in therapy of 4 weeks resulted in higher rates of SVR compared to that of conventional PegIFN/RBV therapy in relapsers (83% without lead-in, 88% with lead-in vs 24%), in partial responders (59%, 54% vs. 15%), and in null responders (29%, 33%, and 5%). Response-guided therapy was not investigated in this study for telaprevir in previously treated HCV genotype 1 patients[4].

Patients with prior virologic relapse may be treated with the response-guided therapy paradigm used for treatment-naive patients. In contrast, those with prior partial and null response should be treated for 48 weeks (12 weeks triple therapy followed by 36 weeks of PegIFN/RBV).

Treatment monitoring and DAAs resistance

There is no sufficient evidence for benefit of lead-in therapy. A comparison of the lead-in and non-lead-in groups in the boceprevir phase 2 study failed to demonstrate significant difference in SVR rates. In addition, in telaprevir REALIZE clinical trial for treatment-experience HCV genotype 1 patients, SVR rates of lead-in and non-lead-in group were also similar [4]. However, the boceprevir phase 2 trial demonstrated a tendency for a higher rate of virologic breakthrough in non-lead-in group than in lead-in group (9% vs. 4%, $p = 0.06$) [29]. On the contrary, and in telaprevir study, there were no differences in the number or type of emerging viral variants between the lead-in and non-lead-in group [4]. Despite these controversial results, lead-in therapy helped to determine PegIFN-α responsiveness in boceprevir studies. Failure to reduce HCV RNA level of less than 1 log during the 4-week lead-in predicted lower SVR rate [1]. However, a chance for achieving SVR by adding boceprevir still existed, therefore these patients should not be excluded from the therapy with boceprevir.

When treating with boceprevir, HCV RNA level should be monitored at week 8 (week 4 after lead-in therapy). If HCV RNA at week 8 was not detected, it can be determined again at week 24, and if it turned out to be negative, duration of the treatment can be shortened. If HCV RNA at week 8 was detectable, it can be evaluated at week 12. If HCV RNA level at week 12 is > 100 IU/mL, treatment with all three drugs should be stopped. Otherwise, RNA level should be tested again at week 24, and if it turned out to be positive, then the treatment should be stopped.

In case of the treatment with telaprevir, HCV RNA level

should be monitored at week 4, and if it is undetectable, HCV RNA level can be tested again at week 12 in order to consider the shortened therapy. If HCV RNA level at week 4 or 12 was > 1000 IU/mL, all three drugs should be stopped. In addition, treatment with telaprevir should be stopped if there is detectable HCV RNA at week 24.

Inadequate response to the therapy often leads to uncontrolled outgrowth of resistant variants to DAA such as protease inhibitors. HCV resistant to DAA are viral variants that bear amino acid substitutions altering the drug target so as to be less susceptible to the drug's inhibitory activity [30]. Cross resistance between two different DAA that target the same site or function can appear by substitution of amino acids that leads to reduced susceptibility to both drugs.

Managing side effects of DAAs

More frequent adverse reactions are detected in patients treated with triple combination therapy with protease inhibitor along with PegIFN-α and ribavirin. In telaprevir clinical trials, gastrointestinal disorders including nausea and diarrhea, pruritus, rash and anemia were more common in telaprevir using groups [2]. In cases with boceprevir studies, dysgeusia and anemia occurred more common in boceprevir treated groups [1]. When anemia developed during the combination therapy using a protease inhibitor, it is recommended to reduce ribavirin dose. If an adverse event occurs that seems to be related to the protease inhibitor and on-treatment response has occurred, discontinuation of the protease inhibitor with continued PegIFN/RBV is recommended. However, in case where either PegIFN-α and/or ribavirin are to be stopped, the protease inhibitor should be discontinued as well [29].

CONCLUSIONS

For the next several years to come, the only possible option to raise the SVR of HCV genotype 1 patients that are newly treated, and to re-treat HCV genotype 1 patients who did not respond successfully to PegIFN/RBV combination therapy, seems to be the triple combination therapy adding one of DAA to PegIFN-α and ribavirin. Triple combination therapy for HCV genotype non-1 patients who failed to achieve SVR after the combination therapy with PegIFN/RBV may need more evidences to be recommended as standard of care.

Oral antiviral agents can suppress HCV, but no one knows whether combination therapy with DAAs will render immune-based therapies such as peginterferon unnecessary; the answer will come from trials of interferon-free regimens. Although DAAs will change the HCV treatment paradigm, their effectiveness may be significantly limited by the emergence or development of drug resistance.

REFERENCES

1. Poordad F, McCone Jr. J, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1195-1206.
2. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011;364:2405-2416.
3. Sherman KE, Flamm SL, Afdhal NH, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. N Engl J Med 2011;365:1014-1024.
4. Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med 2011;364:2417-2428.
5. Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med 2011; 364:1207-1217.
6. Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature 2009;461:798-801.
7. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature 2009;461:399-401.
8. Moradpour D, Penin F, Rice CM. Replication of hepatitis C virus. Nat Rev Microbiol 2007;5:453-463.
9. Barnes B, Lubyova B, Pitha PM. On the role of IRF in host defense. J Interferon Cytokine Res 2002;22:59-71.
10. Foy E, Li K, Wang C, et al. Regulation of interferon regulatory factor-3 by the hepatitis C virus serine protease. Science 2003; 300:1145-1148.
11. Pawlotsky JM, Dahari H, Neumann AU, et al. Antiviral action of ribavirin in chronic hepatitis C. Gastroenterology 2004;126: 703-714.
12. Herrmann E, Lee JH, Marinos G, Modi M, Zeuzem S. Effect of ribavirin on hepatitis C viral kinetics in patients treated with

pegylated interferon. Hepatology 2003;37:1351-1358.
13. Fried MW, Shiffman ML, Rajender Reddy K, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347:975-982.
14. Lee H, Choi MS, Paik SW, et al. Peginterferon alfa-2a plus ribavirin for initial treatment of chronic hepatitis C in korea. Korean J Hepatol 2006;12:31-40.
15. Park SH, Park CK, Lee JW, et al. Efficacy and tolerability of peginterferon alpha plus ribavirin in the routine daily treatment of chronic hepatitis C patients in korea: A multi-center, retrospective observational study. Gut Liver 2012;6:98-106.
16. Swain MG, Lai MY, Shiffman ML, et al. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. Gastroenterology 2010; 139:1593-1601.
17. McHutchison JG, Lawitz EJ, Shiffman ML, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med 2009;361:580-593.
18. Rumi MG, Aghemo A, Prati GM, et al. Randomized study of peginterferon-alpha2a plus ribavirin vs peginterferon-alpha2b plus ribavirin in chronic hepatitis C. Gastroenterology 2010; 138:108-115.
19. Ascione A, De Luca M, Tartaglione MT, et al. Peginterferon alfa-2a plus ribavirin is more effective than peginterferon alfa-2b plus ribavirin for treating chronic hepatitis C virus infection. Gastroenterology 2010;138:116-122.
20. Okazaki T, Yoshihara H, Suzuki K, et al. Efficacy of interferon therapy in patients with chronic hepatitis C. comparison between non-drinkers and drinkers. Scand J Gastroenterol 1994;29: 1039-1043.
21. O'Brien TR, Everhart JE, Morgan TR, et al. An IL28B genotype-based clinical prediction model for treatment of chronic hepatitis C. PLoS One 2011;6:e20904.
22. Puoti C, Magrini A, Stati T, et al. Clinical, histological, and virological features of hepatitis C virus carriers with persistently normal or abnormal alanine transaminase levels. Hepatology 1997;26:1393-1398.
23. Missale G, Cariani E, Lamonaca V, et al. Effects of interferon treatment on the antiviral T-cell response in hepatitis C virus genotype 1b- and genotype 2c-infected patients. Hepatology 1997;26:792-797.
24. Singal AG, Volk ML, Jensen D, Di Bisceglie AM, Schoenfeld PS. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. 2010;8:280-288.e1.
25. Morgan TR, Ghany MG, Kim H-, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Hepatology 2010;52:833-844.
26. Anonymous EASL clinical practice guidelines: Management of hepatitis C virus infection. J Hepatol 2011;55:245-264.
27. Yang PL, Gao M, Lin K, Liu Q, Villareal VA. Anti-HCV drugs in the pipeline. Curr Opin Virol 2011;1:607-616.
28. Ramachandran P, Fraser A, Agarwal K, et al. UK consensus guidelines for the use of the protease inhibitors boceprevir and telaprevir in genotype 1 chronic hepatitis C infected patients. 2012;35:647-662.
29. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB, American Association for Study of Liver Diseases. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the american association for the study of liver diseases. Hepatology 2011;54:1433-1444.
30. Clavel F, Hance AJ. HIV drug resistance. N Engl J Med 2004; 350:1023-1035.