pISSN 2287-2728
eISSN 2287-285X

CMH

Editorial

http://dx.doi.org/10.3350/cmh.2015.21.2.122
Clinical and Molecular Hepatology 2015;21:122-124

Hepatitis C virus infection in patients with hemophilia in Korea: Is antiviral therapy effective and safe?

Woo Sun Rou and Byung Seok Lee

Division of Gastroenterology, Department of Internal Medicine, Chungnam National University School of Medicine, Daejeon, Korea

Keywords: Hepatitis C; Hemophilia A; Peginterferon; Ribavirin; Korean

See Article on Page 125

Hepatitis C virus (HCV) infection is often observed in hemophilic patients who received a blood transfusion of clotting factor concentrates before the mid-1980s, and this increases comorbidity and mortality rates.[1] About 80% of HCV-infected patients have chronic HCV infections, and at least 20% develop end-stage liver disease (ESLD).[2,3]

In Korea, anti-HCV positivity in 1999 was reported to be 49.1% and 47.9% for hemophilia A and B, respectively; since then, it has steadily decreased to 40.1% and 34.1% in 2005 and 33% and 23.8% in 2012.[4] However, among hemophilic patients with anti-HCV positivity, about 31% were positive in HCV RNA testing, and about half remain untreated.[5] A cross-sectional study on the prevalence of hepatitis C and the use of antiviral treatment among patients with hemophilia in the Netherlands showed that about 68% of patients remained untreated. The reasons for non-treatment included the fear of unpleasant side effects of antiviral treatment by the patients (46%), normal liver enzyme values (45%), and doctors' beliefs that the treatment was not very effective (35%).[6]

The response rate of hemophilic patients to interferon (IFN) monotherapy treatment was reported to be low, with a sustained virologic response (SVR) of about 20% (6.5-47.6%); combination therapy of IFN plus ribavirin showed a higher SVR than IFN monotherapy at about 36% (17.7–50.0%).[1,7] Reasons for the low SVR with IFN monotherapy compared to non-hemophilic patients include a long duration of HCV infection, male gender, greater prevalence of HCV genotype 1, and high levels of viremia.[7] In many studies, combination therapy of pegylated interferon (PegIFN) plus ribavirin resulted in variable treatment response rates due to differences in ethnicities and comorbidities in the patients enrolled. In those studies, the rate of SVR was generally high, at about 49-63% (33-51% in genotype 1/4, 71-86% in genotype 2/3) and showed no difference compared to non-hemophilic patients.[1,3,8-11] Also, severe thrombocytopenia and bleeding tendency, side effects to be considered with the treatment, showed no difference in hemophilic patients compared to non-hemophilic patients[11]; major bleeding has not been reported in hemophilic patients.[9,10,12]

Recently, Fransen van de Putte et al.[13] compared patients with inherited bleeding disorders (including mainly hemophilia) who either did or did not receive antiviral therapy. The rates of developing ESLD were 0.6%, 1%, 16%, and 19% in the spontaneous clearance group, successful treatment group, never-treated group,

Abbreviations:

ESLD, end-stage liver disease; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; SVR, sustained virologic response

Corresponding author : Byung Seok Lee
Division of Gastroenterology, Department of Internal Medicine, Chungnam National University School of Medicine, 266 Munwha-ro, Jung-gu, Daejeon 301-747, Korea
Tel: +82-42-280-7125, Fax: +82-42-254-4553
E-mail: gie001@cnuh.co.kr

Received : Apr. 23, 2015 / **Revised :** May 10, 2015

and unsuccessful treatment group, respectively.[3] In addition, when successful HCV treatment was carried out, hepatic fibrosis improved.[13] In summary, the treatment effect and frequency of serious side effects, including bleeding, were not different between hemophilic patients and non-hemophilic patients receiving PegIFN plus ribavirin; furthermore, hepatic fibrosis improved, and the rate of developing ESLD was reduced in the treatment group. Accordingly, unless contraindicated, hemophilia patients with HCV infections must be treated with PegIFN and ribavirin.

The effect of HCV treatment in achieving SVR varies based on ethnicity and country; in the case of Korea, the response to PegIFN plus ribavirin is better than for the US or Europe. However, there have been no studies on IFN monotherapy or combination therapy in domestic hemophilic patients. This may be because interest in hemophilia in Korea is low due to the lack of hemophilic patients, with just 2,204 hemophilic patients, 600 anti-HCV-positive cases, and nearly 200 HCV PCR-positive cases.[5] In this issue of Clinical and Molecular Hepatology, Yang et al. analyzed the treatment effect of PegIFN plus ribavirin in hemophilia patients with HCV infection as subjects. The results were very interesting and surprising. The majority (85.6%) of hemophilic patients demonstrated SVR, and when analyzed by genotype, the rates were 82.4% and 91.7% for genotype 1/6 and genotype 2/3, respectively. This indicates the rate of reaching SVR was higher than reported in other studies. The authors reported high compliance, more patients who were younger, few patients with human immunodeficiency virus (HIV) co-infection, and a favorable rate of IL28B polymorphism as the reasons for the high treatment success rate compared to other studies. Many studies have shown that the response to PegIFN plus ribavirin treatment is poorer with older age, HIV co-infection, high viral load, genotype 1, and failure to achieve rapid virologic response (RVR) or early virologic response (EVR).[8-10,14] Additionally, there is a report that Koreans with HCV infection have the IL28B polymorphism, which shows a favorable response to treatment.[14,15]

This study showed that among factors important for achieving SVR, only achievement of RVR was significant upon multivariate analysis. In particular, the genotype, which is known as an important factor associated with SVR, was not statistically significant. However, this may be because the success rates of treatment in both groups were relatively similar and because there were few patients. In addition, the rates of severe thrombocytopenia or discontinuation of antiviral treatment due to thrombocytopenia noted in this study did not differ significantly compared with the results of previous studies on non-hemophilic patients. Additionally, severe bleeding was not reported in patients with hemophilia in this study. Although bleeding is the most worrisome complication in patients with hemophilia, the current findings suggest that it would not be problematic to treat patients with HCV infections who also have hemophilia, as long as the guidelines are carefully followed.

This study is significant in that treatment with PegIFN plus ribavirin was reported for HCV-infected patients with hemophilia for the first time in Korea; moreover, there were no severe adverse events compared to non-hemophilic patients. As studies on HCV infection including more than 100 hemophilic patients are rare, this study is expected to play an important role in the treatment of patients with hemophilia. Since a poorer treatment response has been reported for hemophilic patients with past treatment failure[9] or HIV co-infection[1,16] compared to those without such conditions, further studies are needed on these patients. Protease inhibitors (boceprevir, telaprevir, etc.) have been recently approved for the treatment of HCV genotype 1 infections; in combination with PegIFN plus ribavirin, these may be considered a triple combination therapy as an alternative for such patients.[3,14,17] In several recent case reports, successful results have been reported on protease inhibitor-based triple therapy for HCV infection treatment in patients with hemophilia.[18,19,20] Additionally, combining current approaches with other new direct acting antivirals, such as NS3/4A protease inhibitor, NS5A inhibitor, NS5B polymerase inhibitor, may shorten the treatment period. Furthermore, in the near future, treatment regimens without interferon will be available to patients for whom interferon therapy is contraindicated.

Conflicts of Interest

The authors have no conflicts to disclose.

REFERENCES

1. Franchini M, Nicolini N, Capra F. Treatment of hepatitis C in hemophiliacs. Am J Hematol 2006;81:696-702.
2. Seeff LB. Natural history of chronic hepatitis C. Hepatology 2002;36(Suppl 1):S35-S46.
3. Fransen van de Putte DE, Makris M, Fischer K, Yee TT, Kirk L, van Erpecum KJ, et al. Long-term follow-up of hepatitis C infection in a large cohort of patients with inherited bleeding disorders. J Hepatol 2014;60:39-45.
4. Yoo KY, Kim SK, Kwon SS, Park SK, Yoon HJ, Lee KS, et al. Life expectancy of Korean haemophiliacs, 1991-2012. Haemophilia

2014;20:e356-e358.
5. Lee KS. A research on Korean hemophilia's prevalence and realities in 2010. Korea Centers for Disease Control and Prevention. 2011.
6. Posthouwer D, Plug I, van der Bom JG, Fischer K, Rosendaal FR, Mauser-Bunschoten EP. Hepatitis C infection among Dutch haemophilia patients: a nationwide cross-sectional study of prevalence and antiviral treatment. Haemophilia 2005;11:270-275.
7. Meijer K, Smid WM, van der Meer J. Treatment of chronic hepatitis C in haemophilia patients. Haemophilia 2000;6:605-613.
8. Posthouwer D, Yee TT, Makris M, Fischer K, Griffioen A, Van Veen JJ, et al. Antiviral therapy for chronic hepatitis C in patients with inherited bleeding disorders: an international, multicenter cohort study. J Thromb Haemost 2007;5:1624-1629.
9. Alavian SM, Tabatabaei SV, Keshvari M, Behnava B, Miri SM, Elizee PK, et al. Peginterferon alpha-2a and ribavirin treatment of patients with haemophilia and hepatitis C virus infection: a single-centre study of 367 cases. Liver Int 2010;30:1173-1180.
10. Mancuso ME, Rumi MG, Santagostino E, Linari S, Coppola A, Mannucci PM, et al; Hepatitis Study Group of the Association of Italian Hemophilia Centers. High efficacy of combined therapy with pegylated interferon plus ribavirin in patients with hemophilia and chronic hepatitis C. Haematologica 2006;91:1367-1371.
11. Honda T, Katano Y, Kuzuya T, Hayashi K, Ishigami M, Itoh A, et al. Comparison of the efficacy of ribavirin plus peginterferon alfa-2b for chronic hepatitis C infection in patients with and without coagulation disorders. J Med Virol 2013;85:228-234.
12. Au WY, Lam CC, Liu CL, Yuen MF. Hepatitis C virus infection in adult Chinese hemophilia patients negative for the human immunodeficiency virus: treatment results with interferon and ribavirin. Int J Hematol 2005;82:259-261.
13. Fransen van de Putte DE, Fischer K, de knegt RJ, Posthouwer D, van Erpecum KJ, Biesma DH, et al. Beneficial effect of successful HCV treatment in patients with inherited bleeding disorders, assessed by liver stiffness measurements. Haemophilia 2012;18:e266-e272.
14. Zoulim F, Bailly F. New approaches to the management of hepatitis C in haemophilia in 2012. Haemophilia 2012;18(Suppl 4):28-33.
15. The Korean Association for the Study of the Liver (KASL). KASL clinical practice guidelines: Management of hepatitis C. Clin Mol Hepatol 2014;20:89-136.
16. Mancuso ME, Rumi MG, Aghemo A, Santagostino E, Puoti M, Coppola A, et al. Hepatitis C virus/human immunodeficiency virus coinfection in hemophiliacs: high rates of sustained virologic response to pegylated interferon and ribavirin therapy. J Thromb Haemost 2009;7:1997-2005.
17. McHutchison JG, Manns MP, Muir AJ, Terrault NA, Jacobson IM, Afdhal NH, et al; PROVE3 Study Team. Telaprevir for previously treated chronic HCV infection. N Engl J Med 2010;362:1292-1303.
18. Singh G, Sass R, Alamiry R, Zein N, Alkhouri N. Hepatitis C treatment with triple therapy in a patient with hemophilia A. World J Clin Cases 2013;1:106-107.
19. Guner R, Tufan ZK. Telaprevir use in a chronic hepatitis C patient with hemophilia. Eur J Gastroenterol Hepatol 2014;26:248.
20. Murata M, Furusyo N, Ogawa E, Mitsumoto F, Hiramine S, Ikezaki H, et al. A case of successful hepatitis C virus eradication by 24 weeks of telaprevir-based triple therapy for a hemophilia patient with hepatitis C virus/human immunodeficiency virus co-infection who previously failed pegylated interferon-α and ribavirin therapy. J Infect Chemother 2014;20:320-324.

http://dx.doi.org/10.3350/cmh.2015.21.2.122