

Pathogenesis and treatment of hepatitis C virus-related liver diseases

Kyuichi Tanikawa

Kurume, Japan

BACKGROUND: Few comprehensive reviews on the pathogenesis of hepatitis C virus (HCV)-related liver diseases have been presented to the present. This article was to review the pathogenesis and treatment of HCV-related liver diseases.

DATA SOURCES: Data presented here are mostly taken from Japanese studies.

RESULTS: HCV infection is characterized by persistent inflammation of the liver and frequent development of hepatocellular carcinoma (HCC) in most cases. These characteristic evidences could be explained by immunological alterations and oxidative stress in the hepatocyte caused by HCV infection. Interferon (IFN) treatment is carried out, at present, not only for the elimination of infected HCV for the treatment of chronic liver diseases, but also for both the prevention of HCC and the treatment of advanced HCC with chemotherapy. The treatment for oxidative stress is also important for non-responders to IFN.

CONCLUSION: It is important to understand the pathogenesis of HCV-related liver diseases for a successful treatment.

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KEY WORDS: hepatitis C virus;
hepatitis C virus-related liver diseases;
interferon therapy

Introduction

At present, it is estimated that there are over 100 million hepatitis C virus (HCV) carriers in the world and most carriers (70%) in Japan are patients with chronic liver diseases. Thus, HCV-related liver diseases are one of the most important liver injuries worldwide. The pathogenesis of HCV-related liver di-

sease is still obscure. Two characteristic clinical evidences for HCV infection have been recognized in recent years. First, once HCV infection occurs, most patients become virus carriers even in adult cases and most of them develop to have chronic liver diseases. Second, once chronic liver diseases develop, few patients are naturally cured and the majority of them develop cirrhosis and finally hepatocellular carcinoma (HCC), which takes approximately 25 to 30 years after HCV infection. Most patients with HCV-related liver diseases may die of HCC. Therefore, the goal of treatments for HCV-related liver diseases is not only to cure chronic liver diseases, but also to prevent the development of HCC.

Pathogenesis of HCV-related liver diseases

The mechanisms of HCV-related chronic liver diseases, by which chronic inflammation persists and most chronic liver diseases finally develop to HCC with a very high frequency, are not well understood. In the pathogenesis of HCV-related liver diseases, the most important fact is that HCV infection occurs not only in hepatocytes but also in lymphoid cells such as dendritic cells.^[1,2] Hence immunological alterations result in insufficiency of HCV specific T cells and natural killer (NK) cell activities.^[3] Such alterations after HCV infection cause persistent HCV infection and insufficient activity of the immunological tumor surveillance system, resulting in a high frequency of HCC development.

Recent attention has been paid to the oxidative stress induced by HCV, especially core protein, on the pathogenesis of hepatocyte injuries.^[4,5] The mechanisms of the oxidative stress have not yet been elucidated. Some reports suggested it be due to mitochondrial changes induced by HCV core protein.^[4] In fact, characteristic changes in these organelles have been observed electron microscopically in hepatocytes.^[6] It is well known that oxidative stress induces inflammatory changes and thus persistent inflammation in HCV-related liver diseases. In addition, possible carcinogenesis in HCV-related liver diseases is caused by oxidative nuclear DNA damage due to oxidative stress, which results in important signal changes. Recent studies^[7,8] have shown that NF- κ B, STAT3, and other signal factors are remarkably activated

Author Affiliations: International Institute for Liver Research, Kurume Research Center, 2432-3 Aikawa-machi, Kurume 839-0861, Japan (Tanikawa K)

Corresponding Author: Kyuichi Tanikawa, MD, PhD, International Institute for Liver Research, Kurume Research Center, 2432-3 Aikawa-machi, Kurume 839-0861, Japan (Tel: 81-942-31-1231; Fax: 81-942-31-1232; Email: tanikawa@kurume.ktam.or.jp)

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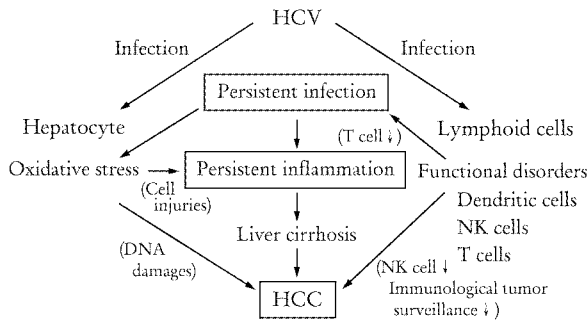


Fig. 1. Mechanism of HCV-related liver injuries.

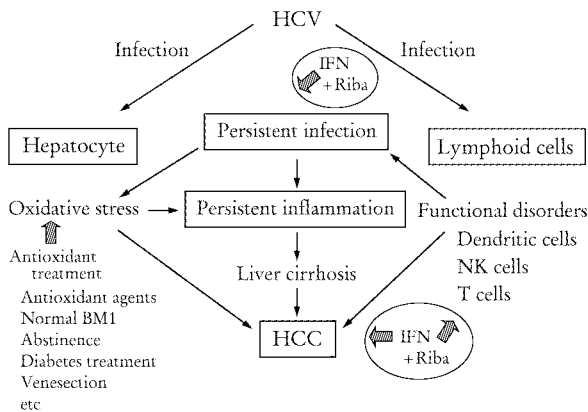


Fig. 2. Pathogenesis & treatment of HCV-related liver injuries.

by HCV core protein. These activations are probably due to oxidative stress in hepatocytes together with an insufficiency of immunological tumor surveillance induced by depressed function of dendritic cells, which is important for the high frequency of HCC development in HCV-related liver diseases (Fig. 1).

Treatment of HCV-related liver diseases

Elimination of HCV from the infected body is the most important factor for the treatment of HCV-related liver diseases. At present, interferon (IFN) treatment for this purpose has been carried out with some success. However, 60% to 70% of HCV-related Japanese patients with genotype 1b and a high titer of viral load are poor responders to IFN and less than 2% to 8% of these patients respond to IFN treatment of 6 months. However, recent clinical trials have shown that about 40% of these patients respond to IFN (or Peg IFN) plus ribavirin combination therapy of 1 year duration (not published). IFN therapy has been improved recently; but a considerable number of HCV-related patients are still left as non-responders to IFN.

For these non-responders to IFN, oxidative stress is one of the most important targets for the treatment of HCV-related liver diseases. Antioxidants such as vitamin

E are reported to be effective.^[9] Ursodeoxycholic acid and glycyrrhizin (strong minophagen C) have been given to non-responders to IFN in Japan with some effect. Recently these agents have been found to have antioxidative effects.^[10,11] It has been reported that obesity is one of the important clinical factors of progression to the advanced stage.^[12] Fatty liver and non-alcoholic steatohepatitis (NASH) are often seen with obesity and these hepatic alterations seen in patients with obesity are associated with oxidative stress in the hepatocyte.^[13] Thus obesity in patients with HCV-related liver diseases is a worsening factor. Indeed, a decreased level of serum ALT has been observed in obese HCV-related patients with weight reduction.^[14] Diabetes is one of the common complications in patients with HCV-related liver injuries.^[15] We have found that insulin-resistance in hepatocytes caused by HCV core protein is an important factor in the development of diabetes in patients with HCV-related liver diseases.^[16] Iron-overload in the hepatocyte is a common complication in patients with HCV-related liver diseases.^[17] Because oxidative stress it induces, phlebotomy is an important choice of treatment for cases of suspected iron-overload. The mechanism by which iron-overload occurs in patients with HCV-related liver diseases has not yet been elucidated. But one report suggested that iron deposit in patients with alcoholic liver injuries be due to up-regulated transferrin receptor expression on the surface of hepatocytes.^[18] A similar mechanism could be considered in patients with HCV-related liver diseases. In alcohol liver injuries the main pathogenesis is oxidative stress and alcohol consumption increases oxidative stress in patients with HCV-related liver diseases.^[19] Hence the prognosis of alcoholics with HCV-related liver diseases is poor. Indeed, a higher incidence of HCC is observed in the HCV+alcohol group compared with the HCV alone group.^[20] Abstinence, therefore, is important for patients with HCV-related liver diseases. Pathogenesis and treatment of HCV-related liver diseases are shown in Fig. 2.

Prevention of HCV-related HCC

It has been well documented that few patients who responded to IFN developed HCC.^[21] Thus, the primary goal for the prevention of HCC is to eliminate the virus from the infected body by IFN therapy. However, administration of IFN for 6 months has been shown to prevent HCC development even in non-responders to IFN.^[22] Though not clear enough the exact mechanisms of this prevention, enhanced NK activity induced by IFN and anti-tumor effect of IFN on small HCC lesions not found by imaging considered. IFN therapy has also been carried out to prevent the second primary HCC lesions after the initial curative treatment for the first primary HCC. Fewer patients had recurrent lesions and

their survival is significantly better after treatment with IFN.^[23,24] IFN treatment itself is meaningful even in non-responders to IFN. At present, combined chemotherapy and IFN has been shown to be effective for the treatment of far-advanced HCC.^[25] In vitro study of IFN on HCC cell lines revealed that most of HCC cells have receptors for IFN and that IFN has anti-tumor effects.^[26] These clinical evidences and basic studies indicate that IFN is an important agent for the treatment of HCV-related liver diseases.

Conclusion

HCV-related liver diseases have increased in number worldwide, and it is important to understand their pathogenesis for a successful treatment.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References

- Muratori L, Gibellini D, Lenzi M, Cataleta M, Muratori P, Morelli MC, et al. Quantification of hepatitis C virus-infected peripheral blood mononuclear cells by in situ reverse transcriptase-polymerase chain reaction. *Blood* 1996;88:2768-2774.
- Kanto T, Hayashi N, Takehara T, Tatsumi T, Kuzushita N, Ito A, et al. Impaired allostimulatory capacity of peripheral blood dendritic cells recovered from hepatitis C virus-infected individuals. *J Immunol* 1999;162:5584-5591.
- Jinushi M, Takehara T, Kanto T, Tatsumi T, Groh V, Spies T, et al. Critical role of MHC class I-related chain A and B expression on IFN- α -stimulated dendritic cells in NK cell activation; impairment in chronic hepatitis C virus infection. *J Immunol* 2003;170:1249-1256.
- Okuda M, Li K, Beard MR, Showalter LA, Scholle F, Lemon SM, et al. Mitochondrial injury, oxidative stress, and antioxidant gene expression are induced by hepatitis C virus core protein. *Gastroenterology* 2002;122:366-375.
- Lerat H, Honda M, Beard MR, Loesch K, Sun J, Yang Y, et al. Steatosis and liver cancer in transgenic mice expressing the structural and nonstructural proteins of hepatitis C virus. *Gastroenterology* 2002;122:352-365.
- Barbaro G, Lorenzo GD, Asti A, Ribersani M, Belloni G, Grisorio B, et al. Hepatocellular mitochondrial alterations in patients with chronic hepatitis C: ultrastructural and biochemical findings. *Am J Gastroenterol* 1999;94:2198-2205.
- Kato N, Yoshida H, Kioko Ono-Nita S, Kato J, Goto T, Otsuka M, et al. Activation of intracellular signaling by hepatitis B and C viruses; C-viral core is the most potent signal inducer. *Hepatology* 2000;32:405-412.
- Yoshida T, Hanada T, Tokuhisa T, Kosai K, Sata M, Kohara M, et al. Activation of STAT3 by the hepatitis C virus core protein leads to cellular transformation. *J Exp Med* 2002;196:641-653.
- Herbay A, Stahl W, Niederau C, Sies H. Vitamin E improves the aminotransferase status of patients suffering from viral hepatitis C: a randomized, double-blind, placebo-controlled study. *Free Rad Res* 1997;27:599-605.
- Mitsuyoshi H, Nakashima T, Sumida Y, Yoh T, Nakajima Y, Ishikawa H, et al. Ursodeoxycholic acid protects hepatocytes against oxidative injury via induction of antioxidants. *Biochem Biophys Res Commun* 1999;263:537-542.
- Yokozawa T, Liu ZW, Chen CP. Protective effects of Glycyrrhizae radix extract and its compounds in a renal hypoxia (ischemia)-re-oxygenation (reperfusion) model. *Phytomedicine* 2000;6:439-445.
- Ortiz V, Berenguer M, Rayón JM, Carrasco D, Berenguer J. Contribution of obesity to hepatitis C-related fibrosis progression. *Am J Gastroenterol* 2002;97:2408-2414.
- Cortez-Pinto H. Oxidative stress in alcoholic and non-alcoholic liver disease. In: Leuschner U, James OFW, Dancycier M (eds). *Falk Symposium 121. Steatohepatitis (NASH and ASH)*, Dordrecht, Boston. London: Kluwer Academic Publishers; 2001:54-61.
- Hickman IJ, Clouston AD, Macdonald GA, Purdie DM, Prins JB, Ash S, et al. Effect of weight reduction on liver histology and biochemistry in patients with chronic hepatitis C. *Gut* 2002;51:89-94.
- Mehta SH, Brancati FL, Strathdee SA, Pankow JS, Netski D, Coresh J, et al. Hepatitis C virus infection and incident type 2 diabetes. *Hepatology* 2003;38:50-56.
- Kawaguchi T, Harada M, Yoshida T, Taniguchi E, Kumemura H, Hanada S, et al. Insulin resistance through down regulation of insulin receptor substrate (IRS)-1 and IRS-2 in patients with chronic hepatitis C virus infection. *Hepatology* 2003;34:456A-457A.
- Bonkovsky HL, Banner BF, Rothman L. Iron and chronic viral hepatitis. *Hepatology* 1997;25:759-768.
- Suzuki Y, Saito H, Suzuki M, Hosoki Y, Sakurai S, Fujimoto Y, et al. Up-regulation of transferrin receptor expression in hepatocytes by habitual alcohol drinking is implicated in hepatic iron-overload in alcoholic liver disease. *Alcohol Clin Exp Res* 2002;26:26S-31S.
- Rigamonti C, Mottaran E, Reale E, Rolla R, Cipriani V, Capelli F, et al. Moderate alcohol consumption increases oxidative stress in patients with chronic hepatitis C. *Hepatology* 2003;38:42-49.
- Miyakawa H, Sato C, Izumi N, Tazawa J, Ebata A, Hattori K, et al. Hepatitis C virus infection in alcoholic liver cirrhosis in Japan: its contribution to the development of hepatocellular carcinoma. *Alcohol Alcoholism* 1993;28,S1A:85-90.
- Yoshida H, Shiratori Y, Moriyama M, Arakawa Y, Ide T, Sata M, et al. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. *Ann Intern Med* 1999;131:174-181.
- Nishiguchi S, Kuroki T, Nakatani S, Morimoto H, Takeda T, Nakajima S, et al. Randomised trial of effects of interferon- α on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. *Lancet* 1995;346:1051-1055.
- Ikeda K, Arase Y, Saitoh S, Kobayashi M, Suzuki Y, Suzuki F, et al. Interferon beta prevents recurrence of hepatocellular carcinoma after complete resection or ablation of the primary tumor – a prospective randomized study of hepatitis C virus-related liver cancer. *Hepatology* 2000;32:228-232.

- 24 Kubo S, Nishiguchi S, Hirohashi K, Tanaka H, Shuto T, Yamazaki O, et al. Effects of long-term postoperative interferon- α therapy on intrahepatic recurrence after resection of hepatitis C virus-related hepatocellular carcinoma. A randomized, controlled trial. *Ann Intern Med* 2001;134:963-967.
- 25 Sakon M, Nagano H, Dono K, Nakamori S, Umeshita K, Yamada A, et al. Combined intraarterial 5-fluorouracil and subcutaneous interferon- α therapy for advanced hepatocellular carcinoma with tumor thrombi in the major portal branches. *Cancer* 2002;94:435-442.
- 26 Yano H, Iemura A, Haramaki M, Ogasawara S, Takayama A, Akiba J, et al. Interferon alfa receptor expression and growth inhibition by interferon alfa in human liver cancer cell lines. *Hepatology* 1999;29:1708-1717.

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Life is not so short but that there is always time enough for courtesy.

— Ralph Waldo Emerson