Hepatitis C Virus Genotypes: Clinical Relevance and Therapeutic Implications

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The incidence of hepatitis C virus (HCV) -related hepatocellular carcinoma (HCC) has been increasing in several countries including Taiwan. There are six main genotypes, each of which contains closely related subtypes. Molecular epidemiological studies have shown marked differences in the genotype distribution by geographical region and between patient groups. HCV genotype 1 may play a role in the development of HCC, although some studies have argued against this. A sustained virological response secondary to interferon monotherapy or interferon/ribavirin combination therapy may reduce the risk of HCC and improve survival in chronic hepatitis C patients. The HCV genotypes are associated with therapeutic response. Rapid virological response is also a predictor of therapeutic response. Although viral characteristics have consistently been shown to be important predictors of treatment response, identification of additional host immune and genetic factors involved in determining the outcome of antiviral therapy is necessary. Newly developed bio-techniques (microarray, proteomes, bioinformatics), drugs, and treatment strategies may elucidate the pathogenesis and improve the therapeutic response in HCV infection. *(Chang Gung Med J 2008;31:16-25)*

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Hepatitis C virus (HCV) is a major etiological agent of chronic liver disease, with an estimated 170 million chronic carriers worldwide.(1) Chronic HCV infection may cause liver cirrhosis and hepatocellular carcinoma (HCC) over the course of two or more decades.(2-4) The incidence of HCV- related HCC is increasing in North America, Europe, Japan, and Taiwan.(5-8) Thus, understanding the risk factors for HCC development and providing effective treatment for HCV are important for preventing progression to end-stage liver disease and HCC. The HCV genotypes may be related to disease progression. Furthermore, HCV genotypes are associated with the response to antiviral therapy. Therefore, further understanding of the clinical relevance and therapeutic implications of the HCV genotype is crucial for

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designing individualized therapies for patients with chronic HCV infection.

Epidemiology of HCV and HCV genotypes

In the United States and most other developed nations, the prevalence of HCV infection is 1-2%. Elsewhere, as in Egypt, the prevalence may be as high as 10-20%. In Taiwan, 1-5% of the general population has HCV.[9-12] In some Taiwanese villages, 50% of the population are positive for anti-HCV.[13,14] Hepatitis C virus contains a positive-sense, single-strand RNA genome approximately 10 kb in length, with a similar genome structure and some sequence homology with pestiviruses and flaviviruses.[15,16] HCV shows substantial nucleotide sequence variation throughout its genome, and at present is classified into six main genotypes, each of which contains closely related subtypes.[17,18] Molecular epidemiological studies have shown marked differences in genotype distribution by geographical region and between patient groups. Genotypes 1, 2 and 3 are widely distributed throughout the USA, Europe, Australia and East Asia (Japan, Taiwan, Thailand and China), whereas geographical distributions of other genotypes are more restricted.[17,19-23] Genotype 4 is largely confined to the Middle East, Egypt and Central Africa. Genotypes 5 and 6 are found predominantly in South Africa and South East Asia, respectively.[17,20,24]

The hepatitis B virus (HBV) carrier rate is 15-20% of the general adult population in Taiwan.[25] Mass HBV vaccination programs have been greatly effective in reducing HBsAg carrier rates and the incidence of HCC in children in Taiwan.[26] As a result, an 80-85% decrease in HCC is anticipated in Taiwanese adults within the next few decades.[27] A previous multicenter study in Taiwan revealed that the percentage of HBV -related HCC in adults has progressively decreased over the past 20 years. However, this has not been due to a decreased incidence of HBV- related HCC but rather to an increased incidence of HCV -related HCC. Similar trends have been reported in Japan[28-30] and the USA.[31] These studies have elucidated the important pubic health issue of preventing viral hepatitis and HCC.

Using an HCV line probe assay for genotyping, it was demonstrated that the predominant HCV genotype in southern Taiwan was 1b (45.5%), followed by 2a/2c (30.9%) and 2b (6.9%).[22] This is compatible with previous studies which used the primer specific method and showed that the prevalence of HCV genotype 1b was around 50-60% and that of 2a around 30% to 40% in southern Taiwan.[23] In contrast, the prevalence of HCV genotype 1b was around 60-70%, followed by 2a at around 10-15% in northern Taiwan in studies using the primer specific method.[21,22]

Natural history of chronic HCV infection

Patients with acute HCV infection are frequently asympatomatic, and only 20-30% of patients show symptoms. Fulminant hepatic failure is rare. Patients with symptoms and women are more likely to clear the virus. Most patients who clear the virus do so within the first 12 weeks. Approximately 50% to 80% of patients who have acute hepatitis C will develop chronic infection. Among these, 20% to 30% will develop progressive disease leading to liver cirrhosis and HCC after 20 years to 30 years of infection.[32-34]

Previous studies conducted both in humans and chimpanzees have clearly demonstrated that various HCV genotypes are not associated with major biologic differences. All the genotypes and subtypes have been found to be both hepatotropic and pathogenic. Importantly, all the HCV genotypes can induce chronic infection.

The role of genotypes in the progression of chronic HCV infection remains controversial.[35-40] Genotype 1b was reported to be associated with more severe liver disease than infection with other genotypes;[36-37] In contrast, different pathogenicity was not observed between genotype 1 and 2.[35,38-40] Although the reasons for these contradictory results are still unknown, several confounding factors may have contributed. Among them, the fact that patients infected with genotype 1b were significantly older than those infected with other genotypes[23] strongly supports the hypothesis that a cohort effect could explain the association between genotype 1b and cirrhosis or HCC. A recent study revealed that the prevalence of genotype 1b in HCC patients was significantly higher than in chronic hepatitis and liver cirrhosis patients. Multiple logistic regression analysis revealed that, after adjusting for age and serum HCV RNA levels, HCV 1b infection was still a significant risk factor for HCC,[22] which was compatible

with previous studies.[36,37] Both the correlation of genotype 1b with age (cohort effect) and intrinsic characteristics of HCV genotypes may be responsible for the association between genotype and the pathogenesis of HCV infection.[22,23] Further large scale and long term follow-up studies are necessary to clarify the relationship between genotype and disease progression. Other risk factors for disease progression and development of HCC are male gender, age at infection, diabetes, hepatic fibrosis (particularly cirrhosis), and greater degrees of hepatic inflammation, iron overload, steatosis, viral factors (viral load and quasispecies), and host genetic factors.[41-44] In addition, other potentially modifiable risks include coinfection with HBV, alcohol abuse, smoking, and obesity.[42]

Treatment of chronic hepatitis C and prevention of HCC

Recent approaches to preventing HCC have focused on eradicating HCV infection (which is responsible for the inflammation and fibrosis), and also on treating or reducing modifiable risks through means such as hepatitis B vaccination and reduced use of alcohol.

Interferon (IFN)-based antiviral therapies have been extensively adopted for treating chronic HCV infection. Over the past several years, accumulating evidence has indicated that IFN-based antiviral therapies improve the histological features of inflammation and reduce the progression of fibrosis in chronic hepatitis C patients.[45-47] Further, antiviral therapies are reducing the incidence of HCC in chronic HCV infection, especially in patients who have achieved a sustained virological response (SVR).[47-51] However, the preventive effects are more apparent before the onset of cirrhosis. Thus, whether antiviral therapies decrease the HCC risk in HCV-cirrhotic patients remains controversial.[48,52-56] Recent meta-analyses of standard IFN monotherapy trials in patients with HCV-related cirrhosis suggest that IFN plays a small but significant role in reducing HCC development.[55,56] In some studies, differences in the HCC incidence between IFN-treated and untreated patients did not attain statistical significance, which may be due to the limited efficacy of IFN monotherapy in HCV-cirrhotic patients.[55,56] Thus, more efficient therapies may affect clinical outcome. Currently IFN-alpha or pegylated-IFN-alpha in combination with ribavirin (RBV) is the most common therapy for chronic hepatitis C.[57-62] A recent study assessed the efficacy of IFN alpha-2b plus RBV therapy in 132 patients with HCV-related cirrhosis, and elucidated the risk factors for HCC. Cox's regression analysis identified a non-SVR, male gender and older age as independent risk factors for HCC, suggesting that achieving an SVR with IFN alpha-2b plus RBV therapy may decrease the incidence of HCC in HCV-cirrhotic patients.[44] A multicenter study in Taiwan further demonstrated by multivariate analysis that preexisting cirrhosis, non-response, HCV genotype-1 and age were associated with HCC. In addition preexisting cirrhosis and non-response correlated with mortality. An SVR secondary to IFN monotherapy or IFN/ RBV combination therapy could reduce HCC risk and improve CHC survival.[63]

To date, no long-term studies have elucidated the effect of the currently recommended regimen of pegylated-IFN and RBV, and no current trials have included untreated control groups. Studies of maintenance pegylated-IFN therapy in virological nonresponders are underway in hopes of demonstrating the effectiveness of this approach in decreasing the risk of HCC development.[64]

Predictors of therapeutic response

The SVR rate using IFN-α monotherapy is 15 to 25%, whereas combined IFN and RBV has doubled the SVR rate. Recent large randomized controlled trials have demonstrated that combined pegylated-IFN alpha and RBV is superior to standard IFN-alpha and RBV and achieved an SVR of 54-65% for genotype 1 and 80-95% for genotype 2 patients.[61,62,65-67] Antiviral therapy for HCV is both expensive and associated with a number of adverse effects. Thus identifying reliable predictors of treatment response is essential. Several factors have been studied to predict the response to antiviral therapy for chronic hepatitis C. Age, gender, duration of disease, histological features (absence of advanced fibrosis), pretreatment alanine transaminase (ALT) levels, RBV and IFN dose, form of IFN, and pretreatment viral characteristics have been found to be predictors of treatment response.[68-71] A recent study reported that significant predictors of SVR were non-genotype 1, low pretreatment viral load, high ribavirin dose (≥ 14 mg/kg), high baseline ALT levels (≥ 120 U/L) and high platelet levels (≥ 150000/mm^3).[71] Of these vari-

ables, genotype is the strongest predictor of an SVR. Present data strongly indicate that HCV genotype is the key determinant of response to IFN-alpha based treatment regimens.[68,72-74] Genotype should be determined in all HCV-infected persons prior to treatment in order to determine the necessary duration of therapy and likelihood of response.[61,66] Patients with genotypes 1 and 4 generally exhibit a poorer response to IFN-based therapy than those with genotypes 2 and 3. HCV genotype 5 appears to be an easily treatable virus, with response rates compatible with those of genotypes 2 and 3 after a 48-week course of therapy.[73,74] Treatment response in genotype 6 HCV patients may be at an intermediate level between that observed in genotype 1 and genotypes 2/3. The optimum duration of treatment (24 vs. 48 weeks) for HCV genotype 6 is unclear and currently under investigation.[73,74]

In the era of treatment with conventional IFN alpha plus ribavirin, the duration of treatment in chronic hepatitis C patients was tailored according to HCV genotype and baseline viremia. HCV patients with genotype 1 and high baseline viremia were treated for 48 weeks, while those with genotype 1 and low baseline viremia, as well as those with genotypes 2 or 3 were treated for 24 weeks.[58,59] Recently, inability to detect HCV-RNA at week 4 of treatment (rapid virological response [RVR]) was reportedly the single best predictor of SVR to pegylated IFN plus RBV therapy. Genotype 1 patients with an RVR may be treated for 24 weeks with pegylated IFN plus RBV therapy.[75] On the other hand, a shorter 12-16 week course of therapy with peg interferon alpha-2b and RBV was reported as effective as a 24-week course in patients with genotypes 2 or 3 HCV who had an RVR at week 4.[65,66] Dynamic changes in HCV RNA during treatment, defined at week 12 as an early virological response (EVR), is useful for identifying individuals unresponsive to therapy.[61,76] Discontinuation of antiviral therapy may be considered in genotype 1 patients when an EVR is not achieved.[61,76]

Resistance to antiviral therapy remains an important and controversial issue, especially in chronic HCV-1b infection. A previous Japanese study suggested that the responsiveness to IFN in HCV-1b infected individuals may correlate with mutations in the amino acid sequence between codon 2209 and 2248 of the NS5A region, commonly known as the "interferon sensitivity determining region" (ISDR).[77] In contrast, data from studies in the United States and Europe do not support this correlation.[78,79] A recent study in Taiwan showed that NS5A-ISDR mutations were correlated with an SVR to combined IFN plus RBV therapy in chronic HCV-1b patients.[80] Our recent study further demonstrated that ISDR mutations correlated with SVR to PegIFNα-2b plus RBV therapy in HCV-1b patients (unpublished data). On the other hand, a similar controversy has been observed between the response to therapy for HCV and mutations in the NS5B region, which exhibit RNA-dependent RNA polymerase activity and are essential in viral replication.[81-83]

Although viral characteristics have consistently proven to be important predictors of response, identification of additional host immune and genetic factors determining the outcome of antiviral therapy is necessary. For example, G protein β3 subunit (GNB3) C825T polymorphism has been shown to affect immune cell function in vitro, and the C825C genotype was found to be associated with non-response in HCV-1 infection.[84] The G-> A transition in the tumor necrosis factor (TNF) α promoter region at position -308 (TNF 308.2) revealed an independent association with an SVR particularly in patients with HCV genotype 1b infection and > 200,000 IU /ml of HCV RNA.[85] Recently, real-time RT-PCR was used to quantify hepatic expression of IFN receptor mRNA (IFNAR2c mRNA) and indicated that hepatic IFNAR2c mRNA may not be useful for predicting the response to IFN plus RBV therapy in patients with HCV-1b infection, but apparently correlated inversely with fibrosis stage and age.[86] Large scale studies are needed to confirm this hypothesis. A recent multicenter study[87] used single nucleotide polymorphism (SNP) of seven genes as a haplotype, i.e.: adenosine deaminase, RNA-specific (ADAR), caspase 5, apoptosis-related cysteine peptidase (CASP5), fibroblast growth factor 1 (FGF1), interferon consensus sequence binding protein 1 (ICSBP1), interferon-induced protein 44 (IFI44), transporter 2, ATP-binding cassette, subfamily B (TAP2), and transforming growth factor, beta receptor associated protein 1 (TGFBRAP1) for the responsiveness trait in 317 chronic hepatitis C patients receiving IFN plus RBV therapy. A prediction model with both the host genetic and viral genotype factors was constructed and demonstrated a sensitivity of

80.7% and specificity of 67.2% for an SVR.

Future study

In addition to the factors mentioned above, other viral factors, and environmental and host factors may influence disease progression and therapeutic effects. Recently developed methods of genomic study using gene chip microarrays have helped to elucidate different signaling pathways in HBV- and HCV- related pathogenesis.[88] Recent proteomic studies have also revealed the potential to help identify biomarkers for the diagnosis of HCC and to determine predictors of therapeutic response for chronic hepatitis C.[89,90] New drugs and treatment strategies, such as proteinase inhibitors, albumin IFN, large dose Peg IFN and large dose RBV have also had an impact on the treatment response for chronic hepatitis C.[91-93]

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C 型肝炎病毒基因型：臨床意義及治療之相關性

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在包括台灣的許多國家，C 型肝炎病毒相關的肝癌發生率正在增加。目前有六種 C 型肝炎病毒基因型，每種有包括相關的亞型。分子流行病學研究發現基因型分佈依地理及病人群而不同。雖然仍然有些爭論，有研究指出 C 型肝炎病毒第一型可能爲發展肝癌角色之一。慢性 C 型肝炎使用干擾素或干擾素合併雷巴威林 (Ribavirin)，若有持續病毒廓清反應可能可減少肝癌發生率，並增加存活率。C 型肝炎病毒基因型與治療效果相關，而快速病毒反應也是治療效果的預測因子，除了病毒特徵已被確認爲治療效果的預測因子外，找出與治療效果相關的宿主免疫及宿主基因等等預測因子也是必要的。新發展的生物科技技術 (如微陣列、蛋白質體學、生物資訊)、新藥及新的治療策略可能可闡明 C 型肝炎致病機轉及促進療效。(長庚醫誌 2008;31:16-25)

關鍵詞：C 型肝炎病毒基因型，臨床意義，治療相關性，干擾素，雷巴威林 (Ribavirin)，宿主因子

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