Management of Chronic Hepatitis C Infection.

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Abstract

Chronic hepatitis C infection is one of the most important causes of cirrhosis and hepatocellular carcinoma in Thailand and worldwide. Hepatitis C virus causes liver inflammation and fibrosis, and may involve other systems such as the kidney and hematological system. The combination of Pegylated interferon and ribavirin is the current standard treatment for chronic hepatitis C infection in Thailand. The treatment has significant side effects, a long duration of treatment, is contraindicated in poor liver function and needs frequent monitoring. The new direct-acting antiviral (DAA) treatment, with and without interferon and ribavirin, produces results in higher response rates, shorter treatment duration and less side effects. These will lead to the new era of hepatitis C treatment and eradication.

Keywords: chronic hepatitis C, extrahepatic manifestation

Hepatitis C virus is one of the most important causes of cirrhosis and hepatocellular carcinoma in Thailand and worldwide. In 1999, WHO estimated global prevalence of hepatitis C virus infection at 3% affecting 170 million people worldwide.[1] In Thailand, the prevalence of hepatitis C infection ranges between 0.94-2.15%.[2,3] Most patients are asymptomatic after acute hepatitis C infection. In acute infection, only 20% will develop jaundice and spontaneous resolution occurs in 15-25%.[4] In patients who become jaundiced, children and young women may clear the infection in up to 45% of cases. Clearance of infection is also influenced by genetic factors and the immune status of the host. HIV coinfection is associated with increased persistence of hepatitis C infection.[5] Chronic hepatitis C infection is defined as persistence of the virus in the blood for more than 6 months after the onset of infection. Spontaneous resolution of chronic hepatitis C infection is quite rare. Most of the patients with chronic hepatitis C infection will be asymptomatic but with fluctuations in ALT levels. It is estimated that 20-30% of chronic hepatitis C infection patients will develop cirrhosis after 20 years of infection.[4] The higher risk of fibrosis progression is associated with obesity, alcohol consumption and co-infection with hepatitis B or HIV infection. The development of cirrhosis increases the risk for decompensation, which include ascites, variceal hemorrhage and hepatic encephalopathy. The rate of developing hepatic decompensation after cirrhosis was found to be 2-5% per year.[6] The risk of hepatocellular carcinoma (HCC) was 1-4% per year in hepatitis C cirrhosis.

Although complications related with cirrhosis and deaths remain important causes of morbidity and mortality from chronic hepatitis C, there are extrahepatic manifestations of chronic hepatitis C which have also been identified. The established (well known) association with chronic hepatitis C are mixed cryoglobulinemia (MC) and B-cell non-Hodgkin lymphoma.[7] Almost 90% of MC patients have active hepatitis C infection and circulating cryoglobulins are found in 40-60% of patient with hepatitis C. However only 5-10% of patients who have circulating cryoglobulins have any clinical consequence. [8] From the retrospective study in Japan, patients with chronic hepatitis C who never received any treatment developed lymphoma in 2.6% compared with none of those whom had been cured from chronic hepatitis C in fifteen years.[9] Other significant extrahepatic manifestations of chronic hepatitis C are porphyria cutanea tarda (PCT), lichen planus and monoclonal gammopathies. The other possible associations are Sicca syndrome, corneal ulceration, thyroid disease, nephropathies, neuropathy, diabetes mellitus and insulin resistance.[7]

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Almost one third of chronic hepatitis C patients with type 2 cryoglobulinemia have renal involvement.[10] Laboratory studies in these patients showed hypocomplementemia and circulating cryoglobulins. The renal disease in chronic hepatitis C infection usually present with glomerular diseases. They can manifest as cryglobulinemic nephropathy, membranoproliferative glomerulonephritis (MPGN), and membranous nephropathy. The most common disease is MPGN. The MPGN is mostly associated with type 2 cryoglobulinemia. The renal involvement in chronic hepatitis C could also present with proteinuria, microscopic hematuria, hypertension, acute nephritis and nephrotic syndrome.[10] Patients with hepatitis C infection should be tested at least once a year for kidney function, including measurement of urinary protein and estimate glomerular filtration rate.[11] If there is evidence of renal abnormalities, patients should be tested for cryoglobulins, complement levels and rheumatoid factor. A kidney biopsy should be considered in patients with significant proteinuria or impaired renal function.

Hepatitis C virus has high mutation rates that result in genetic variation. There are six major genotypes of hepatitis C virus with numerous subtypes. Genotype determination helps to determine the treatment regimen, duration and predict the outcome of treatment. However, genotype does not influence the severity of liver disease such as fibrosis or progression to cirrhosis. There are different genotypes predilections in each part of the world. Genotype 1 is most common in the United States (60-75%) and in the world (42.6%).[12] In Thailand, genotype 3 is the most common (50-60%) followed by genotype 1 and 6.[13] The treatment goals for viral hepatitis B and C infection have some minor differences. The goals for both viral hepatitis would be to prevent patients from cirrhosis and its complication including hepatocellular carcinoma. For chronic hepatitis B infection, the aim is to suppress the number of virus but this occurs with a low probability of getting cured. However, we are able to eradicate chronic hepatitis C virus and cure the patients from the disease with our current treatment. The success of the treatment is the sustained virologic response (SVR) which is defined by the absence of the virus detected by polymerase chain reaction twenty-four weeks after finishing the treatment. Long-term follow up of patients who achieved SVR almost all demonstrate virological negativity (99%)[14] and are thus consider cured. The current standard treatment for chronic hepatitis C in Thailand is peginterferon and ribavirin. The treatment consists of weekly subcutaneous dose of pegylated interferon and twice-daily ribavirin. The treatment duration and outcome depends on the patient's genotype. The treatment durations are either 24 or 48 weeks. In Genotype 1, the treatment duration is 48 weeks which results in an overall SVR of 40-56%.[15,16] For genotype 2 and 3, the duration of treatment is only 24 weeks. The SVR rate for genotype 2 and 3 is 60-84%.[15] Genotype 4, 5 and 6 also need 48 weeks of treatment, with the SVR of 55-64% for all three genotypes. The positive predictors of response to treatment are non-genotype 1, low initial viral load, higher ALT, absence of advanced fibrosis and younger age. The other important predictor of outcome is the rapidity of viral clearance (rapid viral response or RVR) during therapy. The definition of RVR is HCV RNA undetectable after 4 weeks of treatment. Patients who achieve RVR in all genotypes have higher chance of achieving SVR, up to 88-100%.[17] However only 16% of genotype 1 and 60-71% of genotype 2 or 3 achieve RVR when treated with pegylated interferon and ribavirin.[17]

Treatment with pegylated interferon and ribavirin are contraindicated in decompensated cirrhosis due to high rates of morbidity and mortality. There are many side effects from the treatment, which varies from mild flu-like symptoms to severe life threatening events that could lead to termination of treatment. There are some common side effects such as fatigue, myalgia, flu-like symptoms, anorexia, diarrhea, depression or irritability. In addition, laboratory abnormalities can occur and include anemia, neutropenia or thrombocyto penia. These side effects from treatment are the most important causes of premature discontinuation of therapy. In recent years, new, safe and effective interferon-free treatments for hepatitis C using direct-acting antiviral agents (DAA) have become standard regimen for many countries. The HCV genome encodes a polyprotein of 3000 amino acid, which is cleaved by host and viral protease.[18] The polyprotein is used to produce the virus particle, supported particle, envelope glycoprotein and viral RNA replication.[19] The identification of the non-structural proteins of HCV virus (p7, NS2, NS3, NS4A, NS4B, NS5A and NS5B) serves as targets for therapy. DAAs target the critical enzymes in the replication of hepatitis C virus. However, there are some issues with the development of drug resistant virus in part due to the error-prone nature of HCV RNA replication. This article will only mention some of the new DAAs that are currently available or are soon to become available in Thailand.

Sofosbuvir

Sofosbuvir is the first approved nucleotide NS5B polymerase inhibitor.[20] The combination therapy of pegylated interferon, ribavirin and sofosbuvir for 12 weeks had resulted in SVR of 90% in previously untreated hepatitis C genotype 1,4,5, and 6 infections. These results could reduce the interferon exposure time to patients and improve outcomes. The interferon-free regimen consists of sofosbuvir and ribavirin. In genotype 2, after 12 weeks of sofosbuvir and ribavirin, SVR rates were above 90% in treatment naïve and 78% in treatment-experienced cirrhotic patients.[18,21,22] In genotype 3, a longer duration of treatment with combination of sofosbuvir and ribavirin is needed to get a higher SVR almost comparable to genotype 2. After 24 weeks of sofosbuvir and ribavirin in genotype 3, SVR rates were 91% in non cirrhotic and 68% in cirrhotic groups.[21]

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Ledipasvir

Ledipasvir is an NS5A inhibitor with potent activity against hepatitis C genotype 1. The treatment is given daily through fixed-dose combination with sofosbuvir. The SVR rates after 12 weeks of treatment with combination drugs were above 90% in treatment naïve patients and treatment experienced patients without cirrhosis.[23,24] The SVR rate also above 90% after 24 weeks of the combination drugs for treatment-experienced cirrhotic patients. The combination treatment of sofosbuvir, ledipasvir and ribavirin has been studied in patients with cirrhosis with moderate to severe liver impairment, post liver transplantation with, without cirrhosis and fibrosing cholestatic hepatitis.[25] The SVR rates in patients with cirrhosis and liver impairment were 86-89%. In the post transplantation without cirrhosis or compensated cirrhosis SVRs were 96-98% and in post transplantation with severe liver impairment the SVRs were 60-75%. All 6 patients who had fibrosing cholestatic hepatitis achieved SVR.

Daclatasvir

Daclatasvir is an NS5A inhibitor with pangenotypic activity with pharmacokinetic profile allowing once daily dose. Daclatasvir can be used in combination with sofosbuvir in treatment of chronic hepatitis C either with or without ribavirin. Treatment in genotype 3 with daclatasvir and sofosbuvir for 12 weeks resulted in a SVR of 90.1% and 86.3% in treatment naïve and treatment experienced patients.[26] Daclatasvir with sofosbuvir has been recommended as an option for treatment of chronic hepatitis C genotype 1-6 in Thailand.[27] The combination of daclatasvir, sofosbuvir for 12 weeks has been recommended for genotype 1-6 non-cirrhotics. To treat cirrhotic patients with genotype 1,3,4,5 and 6 combinations of daclatasvir and sofosbuvir for 24 weeks or daclatasvir, sofosbuvir and ribavirin for 12 weeks were recommended.

Liver transplantation and hepatitis C

In the past if patients presented with decompensated cirrhosis from hepatitis C with symptoms such as ascites or hepatic encephalopathy, the only treatment option would be liver transplantation. Interferon and pegylated interferon are contraindicated in decompensated cirrhosis. Hepatitis C infection universally re-infected the liver after transplantation with faster progression of fibrosis compared to non-transplanted patients. Treating patients post-transplantation with pegylated interferon and ribavirin have significantly more side effects than non-transplant patients and requires intensive monitoring compared to non-transplanted patients. In the new era of DAA, we are able to treat decompensated cirrhosis patient who are on the waiting list for liver transplantation and also those who are not candidates for liver transplantation. Patient with undetectable HCV RNA virus on treatment with sofosbuvir and ribavirin more than 30 days prior to transplantation have a low risk of recurrence of hepatitis C infection post transplantation.[28] In addition, patients who are not candidates for liver transplantation who achieve SVR may improve their liver function and overall survival rate.

Thais have increased awareness of chronic hepatitis C infection. In the past, the treatment with pegylated interferon and ribavirin was expensive. Currently the price of the treatment has gone down significantly and has become more available to Thais under the universal health care plan. The treatment outcome is still not satisfactory and only a limited number of physicians can prescribe and handle the side effects of the treatment. In the new era of DAA, there will be less side effects and it will be easier to monitor. If the treatment becomes less expensive in the future, we might be able to eradicate hepatitis C from our country.

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