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Predictors of Sustained Virologic Response (SVR) of Chronic Hepatitis C

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Several small studies have reported lower response rate to interferon alfa and ribavirin among subgroups of patients with chronic hepatitis C infection compared with those who have sustained virologic response (SVR). The increased prevalence of infection with hepatitis C virus (HCV) genotype 1, and 4 which have lower response rate compared with genotypes, 2 and 3, was suggested as the cause.

This is a review of some factors, which has been suggested to cause low response among subgroups of patients with chronic hepatitis C.

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World Health Organization (WHO) estimates that about 170 million people, 3% of the world's population are infected with hepatitis C virus (HCV). One hundred and thirty million chronic HCV carriers are at risk of developing liver cirrhosis and/or liver cancer. It is estimated that three to four million persons are newly infected each year, 70% of whom will develop chronic hepatitis. HCV is responsible for 50-76% of liver cancer and two thirds of liver transplants in the developed world[1]. Chronic hepatitis C (CHC) virus infection is the leading cause of chronic liver disease worldwide.

The prevalence of hepatitis C virus (HCV) infection in western countries including Australia and the United States is approximately 1%[2,3]. It is more common in Asian countries. In Asians, HCV prevalence rate is approximately 6%[4,5]. Populous nations in the developed world with relatively low rates of HCV seroprevalence include Germany (0.6%), Canada (0.8%), France (1.1%), and Australia (1.1%), Japan (1.5-2.3%), and Italy (2.2%)[3,6-13]. China, whose citizens account for one fifth of the world's population, has a reported seroprevalence of 3.2%[14]. In India, which has an additional one-fifth of the world's population, one community-based survey reported an overall rate of 0.9%[15]. Indonesia's rate is 2.1%, but is based on serosurveys of voluntary blood donors[16]. In Pakistan, the reported rates ranged between 2.4% and 6.5%[17-20]. Egypt, with an estimated population of 83 million, has the highest reported seroprevalence rate of 22%[21,22].

Chronic infection with hepatitis C virus (HCV) is a common cause of cirrhosis and hepatocellular carcinoma worldwide and spontaneous remission of the disease seems to be rare[23]. The current treatment for HCV infection is peginterferon alfa combined

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with ribavirin and administered for 24 weeks (for HCV genotype 2 or 3) or 48 weeks (for HCV genotype 1and 4)[24]. The two-drug regimen achieve about 40% sustained virological response (SVR) for HCV genotype 1 and 4 and 80 % of genotype type 2 and 3[25,26].

In subgroups of population, the rate of sustained virologic response is even lower, including among black patients, who have a reported rate of sustained virologic response of 19%[27].

There have been few studies of the natural predictors of sustained virologic response (SVR) of chronic hepatitis C patients.

The aim of this review is to evaluate the three important categories of sustained virologic response (SVR) of chronic hepatitis C: 1) Viral factors (genotype and viral load), 2) Host factors (age, race, coinfection, weight, insulin resistance), and 3) Disease related factors (bridging fibrosis or cirrhosis and steatosis).

1. VIRAL FACTORS (Genotype and Viral Load)

The most important predictors of a sustained virologic response following combination therapy of peginterferon and ribavirin are the HCV genotype (higher response in those with genotypes 2 and 3 compared with 1 and 4) and, to a lesser extent, viral load (higher response in those with a baseline viral load $\leq 2 \times 10^6$ copies/mL [approximately 800,000 IU/mL])[28-31].

The optimum treatment for patients with HCV genotype 1 or 4 infection is 48 weeks of pegylated interferon and ribavirin 1000 or 1200 mg/day. Genotype 2 or 3 may be treated with a lower dose of ribavirin (800 mg/day) and for 24 weeks. These findings are reflected in treatment guidelines for chronic hepatitis C[32-34]. The treatment with peginterferon and ribavirin for 24 weeks could achieve SVR rate of 80-93% in patients with HCV2 or HCV3[35]. Genotype 1 and 4 are less amenable to treatment than genotypes 2 or 3. Recent therapeutic trials showed that SVR rate is less common in patients with genotype 1 and 4 infections, higher HCV RNA levels, or more advanced stages of fibrosis.

In two trials using pegylated interferon and ribavirin, SVR rates of 42 and 46% were achieved in patients with genotype 1 and 4 compared to rates of 76 and 82% in patients with genotypes 2 and 3[36]. In a recent study, 24-week course of pegylated interferon and ribavirin was found to be as effective as 48-week course in patients with genotypes 2 and 3 (SVR rates of 73 to 78%). A reduced ribavirin dosage of 800 mg daily appeared to be adequate for patients with genotypes 2 and 3, but standard dosage of 1000 to 1200 mg daily yielded better response rates in patients with genotype 1 and 4[36]. Therefore, 24 weeks of treatment and 800 mg dose of ribavirin appears to be sufficient for genotypes 2 and 3, while patients with genotype 1 and 4 need 48 weeks of treatment and standard doses of ribavirin.

Early viral response (EVR) is defined as a minimum of 2 log decrease in viral load during the first 12 weeks of treatment; it is predictive of SVR and should be a routine part of monitoring patients with genotype 1 and 4. Patients who fail to achieve EVR at week 12 of treatment have only a small chance of achieving SVR even if therapy is

continued for a full year. Treatment need not to be extended beyond 12 weeks in these patients[36]. Although SVR is difficult to correlate with improved survival, because of the necessity for long-term follow up, the absence of detectable serum HCV RNA has been associated with resolution of liver injury, reduction in hepatic fibrosis, and less likelihood of relapse of the HCV infection[36].

von Wagner et al showed that patients chronically infected with HCV-2 and HCV-3 and pretreatment of HCV-RNA level equal or below 800,000 IU/mL can be treated for only 16 weeks with peginterferon alfa-2a and ribavirin without compromising the chances for a sustained virologic response. The data of von Wagner study were less conclusive for HCV-3–infected patients with a pretreatment viremia above 800,000 IU/mL[37]. Additional trials are required to optimize treatment duration in these patients[37].

Genotypes 2 and 3 are far more sensitive to interferon, the sustained response rates are higher and shorter courses of therapy is more effective than in patients with genotype 1. Nonetheless, the EVR definition described previously for the overall group appears to be the best early endpoint for all patients, regardless of genotype with negative predictive value of 99% for genotype 1 and 91% for genotype 2 or 3. Although 96% of patients with genotype 2 or 3 meet early response criteria, an even earlier assessment of response was not possible because of the poor negative predictive value. The high EVR at 12 weeks in patients with genotypes 2 and 3 raises the question of whether it is cost effective to perform virological testing during treatment or not[38,39].

2. HOST FACTORS (Age, Race, Coinfection, Weight and Insulin Resistance)

Age

The combination therapy with PEG-INF alfa-2a and RBV, if tolerated and completed, is effective in treating chronic HCV-4 patients especially if they are younger than 40 years age, have no previous interferon therapy and have lower pre-treatment AST level; the mechanism(s) underlying this is unknown[40,41]. However, it may be related to the development of an intrinsic or immunological resistance to the direct anti-viral effect of interferon. Interferon-inducible protein 10 KDa (IP-10), which is a chemokine produced by hepatocytes that targets T-lymphocytes, natural killer cell and monocytes was recently identified[42,43]. Elevated serum levels of IP-10 before treatment of HCV infection were reported in patients not achieving SVR[44,45]. A recent study confirmed that pretreatment IP-10 levels predict SVR in patients infected with HCV genotype 1, even in those with higher BMI and viral load[46]. Thus, assessment of pretreatment IP-10 may help in identifying patients for whom current therapy is beneficial. This needs to be tested in patients infected with HCV-4.

Race

Kenneth K Yan et al retrospective study, confirmed that in CHC ethnicity is an important variable influencing response to antiviral therapy[47]. In that study, the Asians infected with HCV genotype 1 revealed that the overall SVR approached 70% and those with genotype 1 CHC were more likely to respond favorably to antiviral therapy compared to Caucasians[47].

A summary of six major trials demonstrated that African Americans have a lower response rate to interferon-based therapy compared with whites[48]. Data from various clinical trials suggest that patients of different ethnicities may vary in their responses to interferon-based therapy. Compared with whites, African Americans appear to have lower response rates, whereas Asians and Hispanics may have a more favorable response[48-55].

The different response to therapy is possible because the natural progression of hepatitis C may differ among ethnic groups. African Americans may have a slower progression to fibrosis, while Hispanics may have a more rapid progression[56-58]. The etiology of the different therapeutic outcomes between African Americans and whites is unknown. Genetic or immunologic differences may be involved. There may also be differences in class II human leukocyte antigen alleles, cytokine profiles and Th-1 response (T-cell mediated immunity)[59-61]. It was found that African Americans had different class of human-leukocyte antigen alleles from Caucasians, which could have accounted for their worse SVR. Further, viral kinetics studies have shown that African Americans exhibit significantly lower interferon effectiveness and achieve a lower reduction in HCV RNA in the first 24 hour of treatment. It was also noted that African Americans had different pretreatment cytokine profiles. While they mounted a more robust HCV-specific CD4 Th1 proliferative response, it did not translate into a higher rate of IFN-gamma production. The significance of these studies is that the impact of ethnicity on treatment response is more likely to be related to host factors, particularly to genetic differences in immune regulation rather than environmental factors[47,59-63].

Coinfection

The prevalence of coinfection and human immunodeficiency virus (HIV) in HCV ranged from 4 to 92%. Since the introduction of potent antiretroviral therapy, liver disease due to HCV coinfection has become a major source of mortality among HIV infected persons[64-66]. The progression of liver disease appears to be accelerated in such persons[67]. The information on the tolerability and efficacy of peg-IFN plus ribavirin in HIV-infected individuals with CHC is rather scarce and limited to preliminary information derived from ongoing trials[68-72].

The final results of a trial conducted in Spain on HIV-infected individuals with CHC treated with peg-IFN plus ribavirin having HCV genotypes 2 or 3 were extended to 12 months in those infected with HCV genotypes 1 or 4[73,74]. The relatively low rate of sustained virological response which is 20% in this trial might be explained by short duration of therapy (6 months) and patient carrying HCV-1 and/or low dose of Ribavirin (800 mg BD).

Pérez-Olmeda et al showed that treatment with peg-IFN plus ribavirin is relatively well tolerated in HIV/HCV-co-infected patients[75]. The sustained response rate was 35%, which is clearly lower than that seen in HIV-negative counterparts. The short duration of therapy (6 months instead of 12) in patients with HCV genotype 3 could be the explanation for the limited benefit. Moreover, the intrinsic characteristics of HIV infection itself might reduce the activity of peg-IFN and ribavirin, part of which is immuno mediated and may require a well-preserved immune system to work appropriately[75].

European Consensus Conference recommended that HIV co-infected patient is to be treated for 48 weeks, irrespective of the HCV genotype[76]. However, this recommendation might underestimate the higher risk of toxicity, the lower compliance and the cost associated with extended treatment regimens and ignores the fact that a significant number of HCV genotype 2/3 co-infected patients who clear the virus during the first month of treatment[77]. The recommendations that co-infected patients be treated for 48 weeks irrespective of HCV genotype are based on cross comparisons between historical and prospective studies, which were not designed to address optimal treatment duration and it remains to be proven to what extent HIV-positive patients with HCV genotypes 2 or 3 benefit from schedules longer than 24 weeks. In a recent multicenter randomized trial, 128 HCV genotype 2 or 3 co-infected patients treated with peg-IFN and weight-adjusted RBV for either 28 or 48 weeks, failed to show an increased efficacy of prolonging therapy to 48 weeks and the relapse rate was similar in both groups, probably due to drop out. These data underline the importance of compliance in treatment outcome. Hence, strategies favoring compliance and avoiding unnecessary extension of treatment in very early responders might decrease side effects associated with pharmacological interactions and might be more effective than currently recommended strategies. Several studies in HCV genotypes 2 or 3 mono-infected patients have shown that patients with RVR, defined as undetectable HCV RNA at treatment week 4, achieve similar SVR rates with 12–16-week treatment schedules of peg-IFN and weight-adjusted RBV doses, than those treated for 24 weeks[37,39,78,79].

There are several potential explanations for the diminished rates of antiviral response: HCV RNA levels are higher in subjects with HIV co-infection than in those with HCV mono-infection, the cumulative doses of ribavirin received might have been insufficient to prevent relapse and qualitative defects in the cellular immune response. Investigation of new treatment strategies, including the use of dose-optimized ribavirin will be required to improve response rate and decrease relapse rate among patients co-infected with HCV genotype 1 and HIV[80].

Weight

The data suggest that obesity, defined as greater than 30 kg/m2 is a risk factor for non-response to antiviral therapy, independent of genotype and the presence of cirrhosis. Obese patients as judged by their BMI, independent of genotype and cirrhosis, had approximately 80% lower chance of a sustained response to therapy compared with normal or overweight patients[81,82].

Bressler et al has shown that HCV genotype 3a is associated with steatosis independent of body weight. However, individuals infected with genotype 3a, although they may have hepatic steatosis, have an excellent response to antiviral therapy. In those with genotype 3a, hepatic steatosis disappears with loss of viremia. The response of patients with genotype 3a to antiviral treatment indicates that it cannot be hepatic steatosis alone that decreases the antiviral response. The study showed that, even though a BMI greater than 30 kg/m2 predicts the presence of hepatic steatosis, it is only the BMI that remains an independent risk factor for a poor sustained response to antiviral treatment. Furthermore, the presence of hepatic steatosis does not influence a patient's response to antiviral therapy when their BMI is taken into account[81].

There are several mechanisms have been proposed for obesity and decreased rates of SVR in response to treatment with peginterferon plus ribavirin in individuals with hepatitis C. The first mechanism hypothesizes that obesity is an inflammatory condition, resulting in an abnormal immune response to therapy. The second mechanism, obesity causes insulin resistance and hepatic steatosis, which can lead to steatohepatitis and hepatic fibrosis resulting in direct or indirect interference with the effect of interferon on hepatocytes. A third mechanism, obesity results in decreased bioavailability of peginterferon alpha[83-85]. Steatosis leads to an increase in lipid deposits within cells that may cause a functional disturbance by decreasing the contact area between the drugs and the hepatocytes containing the virus, thus causing a reduction in antiviral drug efficacy. Furthermore, the degree of steatosis has been shown to correlate with the severity of fibrosis[86-88].

Insulin Resistance

D'Souza et al in a pilot study, which excluded diabetic patients, suggested that insulin resistance plays an important role in hepatic fibrosis in HCV patients, irrespective of viral genotype. This association even remained when patients with cirrhosis were excluded. Only insulin resistance and older age were independently associated with a worse fibrosis stage in multivariable analysis. Asian HCV-infected patients had significantly higher insulin resistance than Caucasians. In D'Souza study, patients with HCV genotype 3 were independently associated with an increased likelihood of sustained virological response. Non-responders to antiviral therapy had significantly higher insulin resistance than responders. In multivariable regression analysis Asian ethnicity, higher fasting insulin levels, and higher homeostasis model of insulin resistance (HOMA-IR) levels were independently associated with a poor virological response to therapy[89,90].

The mechanisms of insulin resistance in chronic HCV infection are beginning to emerge. Studies from transgenic mice show that hepatic insulin resistance can be induced solely by HCV core protein. This resulted in increased levels of tumor necrosis factor alpha (TNF-α), which prevented phosphorylation of the insulin receptor-insulin substrate 1 (IRS-1) pathway. This defect in the insulin receptor substrate-1 tyrosine phosphorylation has been found in HCV patients' liver biopsies but not in non infected controls[89-96]. Some studies have ascribed the increased insulin resistance to be secondary to the increase of iron deposits such as ferritin in HCV patients. Insulin resistance may cause fibrogenesis by directly stimulating hepatic stellate cells to proliferate or by upregulation of connective growth factor, a cytokine involved in the pathogenesis of fibrosing liver diseases[89-96].

3. DISEASE RELATED FACTORS (Bridging Fibrosis or Cirrhosis and Steatosis)

Liver Bridging Fibrosis or Cirrhosis

IFN therapy alone or in combination with ribavirin is currently the only approved treatment for patients with chronic HCV infection. Patients with chronic infection, who have varying degrees of inflammatory changes and fibrosis, may develop pronounced fibrotic changes, cirrhosis, and hepatocellular carcinoma if left untreated. Progression from the acute infection to cirrhosis may take several years; up to 20% of patients may develop cirrhosis after 20 years. Some patients exhibit a benign stable course over decades, whereas others progress rapidly[97,98]. Decompensated liver

cirrhosis is a contraindication for IFN therapy because of the risk of severe complications[99]. However, many have suggested that even patients with compensated cirrhosis should be denied IFN therapy because of the disappointing sustained response rates[100]. Patients with chronic HCV infection and advanced liver disease usually have poor responses to treatment with interferons[101-104]. In patients with cirrhosis, interferon either alone or in combination with ribavirin, has been used cautiously, largely because it may exacerbate the patients' neutropenia and thrombocytopenia[105].

Everson GT et al assessed cirrhotic and fibrotic patients with chronic HCV treated with IFN[103]. Fibrotic patients had a lower response than non-fibrotic patients had, but both had similar sustained ALT responses. This discrepancy between ALT and HCV RNA responses suggests that cirrhotic patients may clear the HCV without necessarily normalizing ALT.

One hypothesis proposes that by the time hepatitis C causes cirrhosis in the liver, even elimination of the virus cannot alleviate the histological damage. This raises the question of the appropriate endpoint to use when evaluating therapies for HCV: clearance of serum HCV, normalization of ALT, or improvement in liver histology. Previous reports have suggested that cirrhotic patients do not benefit from IFN therapy to the same extent as non-cirrhotic patients. Some researchers have even questioned the wisdom of treating cirrhotic patients at all. However, the studies that reported disappointing results with IFN therapy relied on ALT as endpoint. If HCV is considered infectious disease, the primary goal of treatment is elimination of the virus, subsequently halting or improving histological damage. The use of IFN therapy for virus elimination is as effective in the treatment of cirrhotic patients with HCV as it is in non-fibrotic and fibrotic patients. It remains to be seen which endpoint-clearance of HCV, normalization of ALT, or improvements in liver histology, best correlates with either delayed progression to cirrhosis or prevent hepatocellular carcinoma.

In conclusion, cirrhotic and fibrotic patients with chronic HCV benefit from treatment with IFN to the same degree as non-fibrotic patients if one assesses efficacy by clearance of serum HCV RNA. The presence of cirrhosis may not allow for the complete normalization of ALT values despite viral clearance. In addition, clinically significant histological benefit is also observed among cirrhotic patients treated with IFN. Therefore, the data show that cirrhosis is not an impediment to the treatment of chronic HCV patients with IFN and that cirrhotic and fibrotic patients could benefit from IFN therapy[103,106].

Liver Steatosis

Liver steatosis is observed in approximately 50% of patients infected with hepatitis C virus (HCV)[107,108]. Even after exclusion of the usual causes of steatosis, obesity, diabetes, alcohol, and drugs, the prevalence of steatosis is 30% to 40%[109,110]. Hepatic steatosis is a common histological finding in chronic hepatitis C virus (HCV) infection, found in 40%-70% of patients[111,112]. Patients with hepatic steatosis were slightly less likely to have a sustained response to peginterferon-ribavirin combination therapy than were patients without steatosis (30% versus 46%), although this was not statistically significant. This weak association may have been a result of the confounding association of hepatic fibrosis and steatosis. The degree of fibrosis was

strongly associated with SVR rate, an association confirmed by multivariable analysis[112].

The mechanisms of hepatic steatosis in HCV are thought to be multifactorial. Several possibilities have been proposed including the presence of insulin resistance. Insulin resistance is a key factor in the development of steatosis in non-alcoholic fatty liver disease and has been observed in individuals with HCV, especially genotype 1 infection[113-117].

CONCLUSION

In term of sustained virologic response (SVR) of chronic hepatitis C, treated with peginterferon alfa combined with ribavirin, genotype 1 and 4 have sustained virologic response (SVR) between 40% and 50%, genotype 2 has between 75% and 90% and genotype 3 has between 65% and 80%. Nevertheless, there are some groups of patients who have lower sustained virologic response (SVR) including: African-American 25%-30%, HCV co-infected with HIV 25% and those with advanced liver fibrosis less than 10%. However, the only modifiable factor which can increase sustained virologic response (SVR) is insulin resistance; reduction of resistance before initiation of antiviral therapy may confer improved response of peginterferon therapies.

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