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Predictors of response to chronic hepatitis C treatment

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ABSTRACT

INowadays the standard of care for hepatitis C therapy is based on Pegylated interferon alpha and ribavirin (Peg IFN/RBV). This combination has led to a sustained virological response rate (SVR) of 50 to 80% depending on genotype. This is still low, considering the side effects, overall costs and duration of therapy. So far, strategies to foresee SVR have been described such as genotype, fibrosis stage, viral load and gamma-glutamyltransferase. In addition, new data has recently been provided on predictive factors of SVR like genetic polymorphism related to race, insulin resistance and viral kinetics. This review aims to discuss these predictive factors of therapy that might help the decision about starting or discontinuing therapy in chronic HCV infected patients.

Key words. Hepatitis C. Pegylated interferon α. Predictive factors. Sustained virological response. Genotype.

INTRODUCTION

Currently, the combination of pegylated interferon alpha (PEG-IFN-α) and Ribavirin (RBV) is the treatment of choice for patients with chronic hepatitis C. Unfortunately this treatment is very challenging.

Antiviral treatment is very expensive, often has many side effects, and lasts too long up to 48 weeks for genotype 1 and 4 with a limited sustained virologic response rate (50-60%). Moreover, there is also a group of HCV infected patients that are not good candidates for PEG-IFN/RBV due to systemic decompensated disease, advanced liver cirrhosis, cytopenias, autoimmune disease and/or psychiatric disease.

Although there are new therapies in development, it's likely that IFN/RBV will remain the mainstay of HCV treatment for the near future. Probably IFN/RBV will continue to be administered together with protease or polymerase inhibitors of HCV replication. Thus, due to an overall low response to standard HCV therapy, it would be important to predict during the pre treatment evaluation period those patients who will respond treatment as well as those who will not. In addition, it would also be important to help decide for whom to start treatment and when to stop the therapy.

Predicting sustained virological response (SVR) to HCV treatment before the beginning of therapy is possible by different well known host and virus related factors such as genotype (1 *vs.* non-1), pre-treatment viral load, fibrosis stage, gamma-glutamyltranspeptidase (GGT), age, race, weight and insulin resistance. Other predictive factors can be identified after starting treatment such as the rapid virological response (defined as an undetectable HCV-RNA at 4th week of treatment) and the early virological response (2 log reduction in viral load at week 12).[1-4] However, it's possible that in near future novel techniques such as individual gene polymorphism and protein profile may open new windows for better identification of good and bad responders to chronic HCV therapy.

PREDICTIVE FACTORS OF RESPONSE TO TREATMENT WITH PEGYLATED INTERFERON/RIBAVIRIN

Genotype

Two types of Peg-INF α have been approved for HCV treatment, Peg-INF α α2a (40 KDa) and Peg-INF α2b (12 KDa). Although there are differences in the pharmacological action between them, their side effects and contraindications are identical.

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Table 1. Predictive factors for treatment response in patients with chronic hepatitis C.

Predictive factors	Best response	Worst response
Patients' factors		
Age of infection	≤ 40 yrs	> 40 yrs
Gender	female	male
Race	Caucasians	African Americans
Insulin resistence	HOMA <2.5	HOMA ≥ 2.5
Genetic polymorphism	CC genotype	AA genotype
Liver fibrosis	< 2 (METAVIR)	cirrhosis
Gamma-GT level	normal	high
Virus factors		
Genotype	2 and 3	1 and 4
Viral load	<600.000 IU/mL	≥ 600.000 IU/mL
Rapid virologic response	yes	no
Early virologic response	yes	no
Comorbidities		
Alcohol intake	low	high
Diabetes	no	yes

The main purpose of HCV treatment is the eradication of the virus. Sustained virological response (SVR) is obtained if an undetectable HCV-RNA using a sensitive RNA assay is achieved both at the end of treatment and six months after finishing therapy. Overall, SVR rates for chronic hepatitis have an average of 50 to 55% with differences between the genotypes. One of the first concepts that were learned about predictive factors was the importance of genotype determination. Three large studies on HCV treatment with interferon α and ribavirin showed different rates of RVS (29% and 65%) between genotype 1 and non-1.[5-7] The same difference was observed in the registration studies that compared PEG-INF α/RBV with IFN α /RBV.[2,3]

Genotype 1 is more difficult to treat. A course of 48 weeks of therapy is required to achieve a SVR of 42 - 46%. SVR rates for genotype 2 and 3 patients are 76%-80% with 24 weeks of treatment. Although in many studies data from genotypes 2-3 are analyzed together, recently it has been suggested that this analysis should be done separately since patients infected with genotype 2 respond much better to PEG-IFN α/RBV therapy than those infected with HCV genotype 3.

Von Wagner reported the SVR rate in 153 patients treated with PEG-IFN α 2a 180 μg/week associated with RBV 800 to 1200 mg/day based on body weight.

Different outcomes were obtained with genotype 2 and 3. Genotype 2 was considered a good predictive factor of SVR after 24 weeks of therapy mainly in those patients who had obtained a rapid virological response (undetectable HCV-RNA at week 4). A SVR as high as 100%, was shown in genotype 2 patients who have had a low viral load in the pretreatment period. In this same study, genotype 3 patients achieved a SVR of 85%. These differences were remarkable in patients with high viral load. In this group the SVR was 95% and 59% for genotype 2 and 3 respectively.[8]

Thus, HCV genotype is considered the most important viral predictive factor of SVR to HCV therapy. Genotype 2 patients are the most encouraging subgroup to be treated.

HISTOLOGY (FIBROSIS STAGE)

Clinical trials data suggest that patients with advanced fibrosis do not respond well to HCV therapy. Although these patients are at an increasing risk for on-treatment complications, they most benefit from a successful viral clearance.

The patients with advanced fibrosis are difficult to manage owing to hyperesplenism with leucopenia and thrombocytopenia. Anemia is more frequent among cirrhotic patients and they show signs of fatigue that generally gets worse with interferon use.

SVR in patients with advanced fibrosis (Metavir F3/F4) was achieved in 8% - 44%, depending on the treatment adopted and the intensity of liver dysfunction.[2,3,9,10] The same studies have shown that in patients with mild disease (Metavir F0/F1) the SVR could reach 74% even in genotype 1 patients.

Recently, Bruno et al analyzed the data from three studies with PEG-IFN α2a / RBV that inclu-

ded patients without advanced fibrosis and patients with advanced fibrosis (bridging fibrosis and cirrhosis). SVR rates reduced progressively from 60% to 50% when comparing genotype 1/4 patients without advanced fibrosis to those with bridging fibrosis. In those with cirrhosis the SVR was only 33% (p= 0.0628). Better results were obtained in genotype 2/3 cirrhotic patients that reached a SVR of 57%. In those without significant fibrosis the SVR was 76%. It should be observed that the population included in this study with advanced liver disease still had a normal albumin level and normal platelet count (172 ± 53).[11] Generally, patients with more advanced cirrhosis such as those with portal hypertension, thrombocytopenia or decompensated disease are excluded from most clinical trials. Scarce data are obtained from pre transplant patients treatment; usually a low SVR is described in genotype 1 patients (<10%) and a higher one in genotype 2/3.[10,12,13]

It's important to emphasize that reduced doses of both PEG-IFN/ RBV were prescribed in these difficult-to-treat groups.[10,14]

Portal hypertension may be considered a negative predictive factor of response to HCV therapy when considering Peg Interferon alone or combined with RBV. Di Marco et al performed a randomized controlled trial in 102 HCV patients with compensated cirrhosis and portal hypertension. Fifty-one patients received 1 mcg/kg/week of PEG-IFN α-2b and 51 PEG-IFN α-2b plus 800 mg/day of RBV up to 52 weeks. The SVR was higher in the PEG-IFN/ RBV group compared to monotherapy group (21.6% and 9.8% = 0.6%) but both groups had a modest SVR rate.[13]

INSULIN RESISTANCE

Insulin resistance (IR) could be defined as a reduction of tissue susceptibility to insulin. This process leads to an increase in insulin production to maintain a normal level of glucose. High levels of insulin increase the flux of free fatty acids towards the liver with accumulation of triglycerides in the hepatocyte (steatosis).

HCV infection is associated with IR even in the absence of obesity or diabetes. In chronic hepatitis C patients resistant to PegIFN / RBV therapy, intrahepatic levels of the suppressor cytokine signaling (SOCS 3) are increased. SOCS 3 is a factor promoting the degradation of insulin receptor substrate thus leading to impaired insulin signaling and IR. This phenomenon has been attributed to obesity but might be independently induced by HCV.[15] There is a relation between IR and grade of fibrosis. The prevalence of diabetes in HCV patients in cirrhotic stage is increased.[16] The frequency of IR in patients with HCV genotypes 1 and 4 ranges from 37% to 69% but probably this prevalence depends on the demographic characteristics of the population being studied.[17,18]

Many studies have demonstrated an association between IR and response to HCV therapy with Peg IFN/RBV.[19-21] HOMA index has been utilized as an indication of IR. The cut-off value for HOMA index is between 2 and 2.5. In 2005, a Spanish study by Romero-Gomez including 113 genotype 1 HCV infected patients, reported SVR rates of 61%, 46% and 20% in those with HOMA Index less that 2, from 2 to 4 and higher than 4 respectively.[20] Diabetes and obesity are also associated with lower SVR rates.

There are few studies with drugs that enhance the tissues sensitivity to insulin in association with Peg IFN/RBV in order to increase SVR.[22,23]

Pilot studies with pyoglitazone didn't show any benefit. Metformin was also prescribed in association with PegINF alfa-2a/RBV therapy in a large study but only a trend to increase SVR was observed [24]. A critical note about this study is that metformin was started together with the antiviral treatment and probably IR needs some months of therapy to be reduced. As the first month of therapy with Peg IFN/RBV is very important to the final outcome, one could wonder if by the end of the first month, IR was already corrected in the group of patients with this metabolic disturbance. Large randomized studies with metformin, pyoglitazone or both are necessary to better clarify this subject.

VIRAL LOAD

HCV viral load is not considered a major determinant of disease progression, however it might be an important predictive factor of response to HCV antiviral therapy. SVR is constantly higher in patients with low HCV RNA levels regardless of genotype.

Many studies including genotype 1 and genotype 2-3 patients have shown an association between baseline viral load and SVR. Thus, viral load levels and its kinetics have been used to shorten the treatment duration. This was shown in patients who obtained rapid virological response.[8,25] In genotype 1 infected patient with a baseline viral load less than 250.000 IU/ml who achieved RVR, the SVR rate was higher (92%) despite a short course of 24 weeks of

treatment.[26] Manns et al in an original study[2] that compared Peg IFN/RBV with INF/RBV showed that those with a viral load lower than $2x10^6$ copies/mL had a SVR of 78% compared with a SVR of 42% in those with a viral load higher than $2x10^6$ copies/mL. Nowadays there is a debate about the real definition of a low viral load and who will be the candidates for a reduced duration of treatment based on the fourth week response (RVR).

GAMMA-GLUTAMYLTRANSFERASE

Gamma-glutamyltransferase (GGT) is a liver enzyme usually related to cholestasis or alcohol abuse. GGT levels can be increased in other clinical situations that occur in association with HCV infection like steatosis, ductal lesion and advanced fibrosis.

GGT level is increased in a certain amount of HCV infected patients mainly in those with advanced fibrosis. Normal levels of GGT have been associated with an increased SVR rate mainly in HCV patients without cirrhosis.[27] Villela-Nogueira et al showed that normal levels of GGT were independently associated with a higher response to INF/RBV therapy in genotype 1 patients when compared with patients without abnormal levels of GGT. The same result was demonstrated when HCV infected patients were treated with Peg IFN/RBV, suggesting that low levels of GGT at baseline were a strong predictor of SVR in genotype 1 chronic hepatitis C patients treated with PegINF / RBV for 48 weeks.[28,29]

The exact mechanism of this feature is unknown but so far it has not been related to steatosis, obesity, diabetes, alcohol abuse or advanced fibrosis, due to the fact that the patients included in these studies were non cirrhotic, with normal weight and non alcohol abusers. A recent study suggests that GGT could be increased in HCV patients owing to the oxidative stress caused by hepatic inflammation.

RACE

Several small studies have observed that African Americans (AA) HCV infected patients have lower response rates to antiviral therapy when compared to Caucasians.[30-32] Muir et al compared the SVR rate in a cohort of 100 AA and 100 non Hispanic Caucasian patients with chronic hepatitis submitted to PegIFN/RBV therapy.[33] Baseline characteristics of both groups were similar except for higher weight and higher diabetes prevalence among the AA population. The SVR was higher in the Caucasian group compared to the AA (52% *vs.* 19%). A poor outcome to PegINF/RBV based therapy was equally demonstrated in AA and Hispanic genotype 1 HCV patients. SVR was obtained in only 16% of AA and in 13.7% of Hispanics.[34] Recently results from the Ideal Study, a large comparative study between the two approved Peg IFN, confirmed the lower response rate of AA patients.[35] Another recent study about genetic polymorphism near the IL28B gene encoding interferon lambda-3 showed a lesser frequency of a single polymorphism nucleotide (rs12979860) among AA HCV patients. The CC genotype was associated with higher frequency of SVR to HCV drug therapy.[36,37] This feature could explain the low response rate to interferon therapy according to different races.

GENETIC POLYMORPHISM

The sequencing of the human genome , together with the development of high- technologies that measure the genomic function, have revealed unique opportunities to predict treatment response.

In 2009, three independent genome-wide association study (GWAS) reported single nucleotide polymorphisms (SNPs) near the IL-28B (IFN-lambda 3) region and its association with therapy response.[36,38,39]

Thomas et al reported that the same IL-28B variant described by Ge was also associated with spontaneous viral clearance. They showed that the C/C genotype was associated with resolution of HCV infection in European and African ancestry.[36,37]

McCarthy et al showed that the variant rs12979860 C/C genotype has a 65% sensitivity and a 78% specificity for SVR in genotype 1 chronic hepatitis C patients treated with PegIFN/RBV.[40]

Although the initial results of these studies are exciting, it is not already known what will be the role of these new findings in pre-treatment decisions for patients with chronic hepatitis C.

OTHER PRE-TREATMENT PREDICTIVE FACTORS

The role of alcohol abuse in the response rate to hepatitis C therapy is very difficult to evaluate because heavy drinkers are usually excluded form treatment protocols. Alcohol can reduce the SVR indirectly by increasing HCV replication. This suggests that chronic hepatitis C patients should abstain from drinking before antiviral therapy. Anand et al in a recent large, prospective, multicen-

ter trial, showed that the lower SVR observed among drinkers was related to frequent drug discontinuation in alcohol drinkers.[41]

Iron overload, either genetic or secondary to others conditions has also been a subject of major controversy. There are positive and negative correlations between SVR and intrahepatic iron overload.[42-44] Two recent studies were divergent about the association of a high intrahepatic iron concentration and the presence of HFE gene mutation as a predictive factor of non-response to PegIFN/RBV treatment.[45,46] High levels of ferritin, frequently related to non-response to antiviral therapy may suggest more advanced liver disease or more liver inflammation.

The importance of age as a predictive factor of response to chronic hepatitis C treatment is very difficult to define because mild histological liver disease is more frequent among young patients and advanced liver disease is more prevalent among elderly people. The elderly patient usually has more drug adverse effects, poorer adherence as well as other co morbidities and thus a lesser SVR rate is obtained.

In a recent study, low vitamin D serum levels were related to low response of interferon – based therapy in genotype 1 patients. This feature was more frequent in advanced fibrosis but on multivariate analysis, low 25(OH) vitamin D levels were independently associated with absence of SVR.[47]

Another recent study looked at the association between the development of thyroid diseases and response to HCV therapy. There was a positive and significant association between thyroid disease and viral clearance, but a recently published meta-analysis didn't confirm this finding.[48]

PREDICTIVE FACTORS OF ANTIVIRAL RESPONSE DURING THERAPY

Current AASLD guidelines indicate that early virological response (EVR), defined by having at least a 2 log drop HCV-RNA in the serum on week 12, is an important positive predictive factor for SVR.[2,3,49,50] In the PegIFN alpha - 2a/RBV registration study, the SVR was 67% in those that achieved EVR. On the other hand, only 3% of patients without EVR achieved SVR. Absence of EVR is the most accurate predictor of treatment failure and a stopping rule for treatment is advisable when patients do not achieve the EVR. Still regarding week 12 viral kinetic aspects, it should be distinguished between a 2 log reduction from baseline viral load (slow responders) and an undetectable viral load at week 12 (complete EVR- cEVR). Pearlman studied 361 slow responders to PegIFNα 2a/RBV and treated them for 48 or 72 weeks.[51] The SVR in the standard treatment arm (48 weeks) was only 18%. In contrast many studies have evaluated the SVR in patients that had obtained a cEVR. A mean SVR reported was 67%.[3,52-55]

A more powerful SVR predictor during genotype 1 HCV therapy is the rapid virological response defined as a undetectable HCV-RNA (<50UI/mL) at week 4.

RVR was reported in only 12-20% of PegIFN/RBV treated patients but these patients obtained a very high SVR (80-100%).[3,52,54,55]

Segadas-Soares reported a high positive predictive value of SVR of 75% among genotype 1 naïve chronic hepatitis C patients treated with PegIFN α-2b/RBV who obtained an RVR.[29] The SVR rate among patients without RVR was as low as 23%. Although in this study the HCV-RNA was performed with a moderately sensitive PCR assay (<600IU/mL), the value of RVR was also significant.

Nowadays there is an increasing debate about the possibility of reducing the treatment length in patients with RVR and low baseline viral load.

Briefly, the tools current available to predict SVR can help simplify the decision about starting or discontinuing treatment in many clinical settings. However, none of them can guarantee an exact prevision.

New antiviral drugs such as protease inhibitors may change the value as well as the interpretation of some of these predictive factors. It's possible that in the near future, the combination of clinical, virological and genomic data may better predict virological response in hepatitis C treatment.

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