Prognostic factors determining the outcome of treatment in chronic hepatitis C

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Abstract

After a brief introduction in terminology and a distinction between predictors and determinants or response to therapy in chronic hepatitis C, a review of the wide literature on this topic is presented. None of the pretreatment variables or combination of them can be used as an absolute predictor of response in individual patients. Prognostic factors can help in clinical practice for informing and counseling patients of the likelihood of response. Information on pretreatment HCV RNA levels and HCV genotype can improve the cost benefit of therapy. Predictors of response should be properly evaluated in terms of positive predictive value, negative predictive value and accuracy. The strongest hitherto predictor of sustained response to any therapeutic regimen in chronic hepatitis is the clearance of HCV RNA during treatment. Recent data suggest that sequencing of several regions of the HCV genome may provide important prognostic information on the outcome of therapy. In complex and difficult to treat subsets of patients with chronic HCV infection, available data on predictors and determinants of the outcome of treatment are limited.

In the treatment of chronic hepatitis C the terms "prognostic factors" or "predictors" and "determinants" of response are frequently applied interchangeably. However, these terms differ significantly both in their origin (etymology) and meaning. Prognosis is a Greek word, meaning prior (pro) knowledge (gnosis). It means that in a given situation you have acknowledge in advance of what is going to happen in the future. This knowledge is usually acquired from the study of certain variables or factors in relation to actual outcome of the disease or its therapy (good or bad prognostic factors). Of course, if prognosis is possible then it can be also spelt out in advance, which means "prediction". Prediction, therefore, a word of latin origin, constitutes the verbal counterpart of prognosis. Moreover, since all knowledge in science should be communicated, "prognosis" and "prediction", though literally different, can be actually used interchangeably. On the other hand, several pretreatment variables found to be associated either with response or no-response to therapy may be of prognostic value, may well predict but do not really determine the outcome of treatment. Most available data indicate that what actually determines if a patient with chronic hepatitis C will achieve or not a sustained response to treatment is : a) the individual sensitivity of the hepatitis C virus (HCV) to the inhibitory effects of the administered drugs and b) the strength of specific host immune responses against HCV induced by therapy. To give two examples : a) the genotype of HCV is a determinant of response to IFN-a therapy but can also be used as prognostic factor and predictor of response, b) the HCV RNA level in serum is a predictor not a determinant of the response. It simply reflects the level of HCV replication in the liver which is the actual determinant of response.

Currently significant efforts are being directed to the understanding of the molecular components and mechanisms of viral sensitivity and resistance to therapy and of specific T and B cell responses against HCV (1-4). But these still remain at the investigational level.

The clinically relevant prognostic factors of the outcome of treatment are numerous and will be reviewed with emphasis on those viral- and host-factors (table I) that may also represent determinants of sustained response (table II).

Many studies have focused on the identification of the profile of the patient with chronic hepatitis C who is likely to respond to treatment. Claimed predictors of

Table I. — **Host factors influencing the natural course of chronic hepatitis C virus infection**

A. INTRINSIC	B. EXTRINSIC
Age at infection	Alcoholism
Gender	Viral co-infections
HLA type	Smoking
Haemophilia	Immunosuppression
Diabetes	Enviromental and geographical ?
Haemochromatosis	
Race ?	

Table II. — **Claimed predictors of response to IFN and IFN+ribavirin treatment in chronic hepatitis C**

1. Age at acquisition of infection	10. HCV genotype
2. Duration of HCV infection	11. Pretreatment HCV RNA levels
3. Sex	12. Viral quasi species
4. Body weight	13. Nucleotide sequence of certain regions of the HCV genome
5. Liver chemisties (AST, ALT, GGT)	14. Several immunological variables
6. Liver necroinflammation	15. Miscellaneous other
7. Liver fibrosis	
8. Presence of absence of cirrhosis	
9. Hepatic iron	

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response to IFN and ribavirin (Rb) therapy in ordinary patients are numerous (5-14) and include age at acquisition and duration of HCV infection, sex, body weight, serum chemistries particularly serum aminotransferases and GGTP levels, extent of liver necroinflammation and fibrosis, presence and absence of cirrhosis, pretreatment levels of hepatic iron, HCV genotypes, pretreatment HCV RNA levels, viral quasi species, nucleotide sequence of certain areas of the HCV genome and several other variables (table II). It is necessary to emphasize that in clinical practice the use of a variable as predictor or response to a certain therapeutic regimen prerequires determination of its positive and negative predictive value and its accuracy. These parameters have not been properly determined for all claimed prognostic factors and need to be also evaluated in the prediction of the outcome of several combination schemes and emerging new therapies. Moreover, it should be remembered that geographic, phyletic, age, sex and other differences may modify significantly the positive and negative predictive value of any variable.

For the time being, all data in the literature indicate that none of the pretreatment variables or combinations of them (table III) is an absolute predictor of response and therefore cannot be reliably used in individual patients (11,15). However, prognostic factors can help in informing and counseling patients on the likelihood of a response. In addition, information on pretreatment HCV RNA levels and HCV genotypes can improve the cost benefit of therapy by increasing the duration of combination treatment to 12 months in naive patients with genotype I or 4 if the level of pretreatment viraemia is more than 2×10^6 copies/ml ; and keeping its duration to 6 months only for lower levels of viraemia and for genotypes 2 and 3 regardless of the levels of viraemia.

Table III. — **A sustained virological response to interferon therapy in chronic hepatitis C has often been associated with**

Mild disease, in particular
* Absence of cirrhosis
** Young age
* Short duration of the disease
** HCV genotypes
** Low level of circulating HCV RNA

The strongest, hitherto, predictor of a sustained response to any therapeutic regimen is the early clearance of serum HCV RNA during treatment or an initial decline by more than 3 log after 4 weeks of therapy (9,10). Approximately 50% of those who clear HCV RNA at week 4 of treatment achieve a sustained response, while a positive HCV RNA has a positive predictive value of no response in 97% of the patients. In this context, a positive HCV RNA at week 4 calls for change in the therapeutic regime. In a study of ours on high dose interferon therapy initiated with a 4 week period with daily administration of IFN it was observed that non detectable HCV RNA at day 7 was associated with a 50% possibility of sustained response while a detectable HCV RNA was associated with only 18% sustained response (16). Moreover, persistence of HCV RNA positivity after week 2 was associated with 0% change for sustained response. Return to normal of serum aminotransferases early during therapy is also a predictor of sustained response but less so than early HCV RNA clearance. Moreover, it may also lead to false clinical conclusions (14).

Recently, sequence of several regions of the HCV genome appears to provide important information on possible molecular predictors and determinants of response (1-4,13,15). These include the interferon (IFN) sensitivity determining region (ISDR) of the NSSA of genotype lb and an area of E_2 which contains a sequence identical to the phosphorylation sites in the IFN-inducible kinase PKR and the translation initiation factor eIF2a, a target of PKR. Baseline expression of IFN receptor genes, immune genetic factors mainly HLA, and pretreatment anti-HCV core IgM levels are also being evaluated as predictors and possible determinants of the outcome of therapy.

In complex and difflcult to treat subsets of patients with chronic HCV infection, the available information on the value of prognostic factors of the outcome of treatment is limited. The studied groups are numerous and include children, patients with normal ALT values at baseline, with cirrhosis, coinfected with other viruses, immunocompromised, multiply transfused, in chronic heamodialysis, transplanted, with extrahepatic manifestations and others. Most studies comprise small number of patients, largely treated with IFN alone with generally low sustained response rates while many of the findings are controversial. However, in general, the prognostic value of sex, HCV genotypes and viral load seems to hold also true in many of these subsets of patients. For example, in HCV-associated cryoglobulinaemia the presence of cirrhosis, HCV genotypes and cryoglobulin levels have been found to be predictors of the outcome of treatment, while no significant association or controversial results have been reported in the case of other factors including age, sex, duration of disease, LFTs and other laboratory abnormalities.

From these data it is clear that the clinically most important topic of prediction of response to therapy in chronic viral hepatitis C and the understanding of host and viral factors determining the course of HCV infection and the induction of sustained virological clearance by therapy has still a long way to go. Clearly it represents a topic of research to be continued in the new millenium.

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