

Predictive factors for response to treatment of chronic hepatitis C

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Several studies have been carried out to identify factors that facilitate identification of chronic hepatitis C patients who are likely to respond to antiviral treatment. Predictive factors are classified into two categories:^{1,2}

- I. predictive factors evident before treatment, and
 - II. predictive factors evident during treatment.
- I. Predictive factors that are evident before treatment are classed into the following categories:
 1. virological predictive factors,
 2. predictive factors associated with the host,
 3. analytical (biochemical) predictive factors,
 4. immunological predictive factors, and
 5. histological predictive factors.
 - II. Predictive factors that are evident during treatment are classed as follows:
 1. virological predictive factors,
 2. analytical (biochemical) predictive factors, and
 3. factors associated with compliance with treatment.
 - I. Baseline predictive factors before and during treatment
 1. Virological predictive factors
 - a. Hepatitis C virus (HCV) genotype
 - a1) HCV genotype 1. The response to treatment with pegylated interferon alfa 2a or interferon alfa 2b plus ribavirin every 24 hours for 48 weeks is 40%.
 - a2) HCV genotypes 2 or 3. The response to treatment with pegylated interferon alfa 2a or interferon alfa 2b plus ribavirin every 24 hours for 24 weeks is 80%.

Sustained responses are maintained for more than 10 years. Persistence of virological and histological responses probably plays a role in recovery from this disease. Patients infected with HCV genotypes 2 or 3 have a four-fold greater probability of responding to treatment than those infected with HCV genotype^{1,3-7,9,10} Hayashi et al.¹¹ conducted multiple regression analyses of data from a co-

hort of 80 patients who were treated with interferon alfa for 6 months and found that HCV viral genotype and viral rate were of significant value ($p = 0.048$ and $p < 0.001$, respectively) for predicting full responses to treatment.

In the study of Tabaru,¹⁶ 25 patients with HCV genotype 2 were treated with interferon for 24 weeks (Group A; $n = 13$) or 6 weeks (Group B; $n = 12$). All patients were virus free upon completion of treatment, but full sustained responses occurred in 53.8% of patients in Group A and 58.3% of patients in Group B. The difference between the groups was significant, suggesting that the duration of treatment may be less than 24 weeks in patients for whom a favorable outcome is predicted.

In a Japanese study published in 1995,¹³ the response rates to treatment with interferon plus ribavirin were 57.78% for individuals infected with HCV genotype 2b, 46.15% for individuals infected with HCV genotype 1a, 47.62% for individuals infected with HCV genotype 2a, and 11.6% for individuals infected with HCV genotype 1b.

The predictive value of early virological response for determining the outcome of long-term antiviral treatment with peginterferon and ribavirin was examined in a randomized clinical study.¹⁴ The subjects of the study were 280 treatment-naïve patients who were chronically infected with HCV genotypes 2 or 3 and who received peginterferon alfa 2b ($1.5 \mu\text{g/kg}$ bodyweight by subcutaneous injection once weekly) and ribavirin (1.0–1.2 g once daily) for 12 or 48 weeks. HCV RNA was undetectable at week 4 in 130 of the patients who received the treatment for 12 weeks. As viremia was present in the remaining 80 patients of this group on week 12, they continued to receive treatment until week 24. An early virological response was detected in 99.2% of patients who were not viremic in week 12, in 81.2% of patients who were still viremic in week 12, and in 81.4% of patients who received treatment for 48 weeks. The corresponding sustained virological response rates 24 weeks after treatment were 89.2%, 78.7%, and 81.4%. The authors affirmed that the symptoms reverted in the majority of HCV genotype 2 or 3 patients who exhibited virological responses after 12 weeks of treatment and that only those who presented with viremia at week 4 benefited from the longer period of therapy.

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In an analysis carried out by Davis et al.,¹⁰ early viral response (week 12) had a negative predictive value of 98% for correctly identifying nonresponders with HCV genotype 1. In patients with HCV genotypes 2 or 3, the predictive value of the early viral response was unreliable because of small sample size. During treatment with pegylated interferon alfa 2a plus ribavirin, only four patients with genotypes 2 or 3 did not have an early viral response. Therefore, it is recommended that in the case of patients with HCV genotypes 2 or 3, treatments should be given for 24 weeks without checking for the presence of the HCV RNA in the serum at week 12.

b. Viral load

Kinetic studies of viral clearance rates have shown that interferon treatment reduces HCV RNA concentrations in serum in two stages:^{8,15,16,34-40,45}

- a sustained virological response associated with fast biphasic viral clearance, which eliminates the virus from the blood during weeks 4 to 12 of treatment, and
- a fast viral clearance that is positively correlated with the low incidence of recurrence in responders at the end of treatment and is an important determinant of the duration and type of therapy required.

A recent study proved that extent of the reduction of viral load within the first 24 hours of administering a single dose of interferon is indicative of the sensitivity of the viral strain to interferon and predicts the response to treatment with a specificity of 100% and a sensitivity of 83%. Patients who do not exhibit early virological responses (HCV RNA reduction of $\leq 2 \log_{10}$ after 12 weeks) do not attain sustained virological responses (negative predictive value = 98%). Therefore, treatment should be discontinued in the absence of an early viral response. Viral clearance rate should be used to define the treatment.^{14,15}

Shigehiko et al.¹⁶ studied HCV dynamics a month before treatment of 141 chronic hepatitis C patients with 6 million IU interferon alfa 2b for 24 weeks. Patients were classified into three groups according to viral load:

group 1: increasing viral RNA level (HCV > 0.20 log copies/mL/month),

group 2: stable RNA level (HCV = 0.20 log copies/mL/month), and

group 3: decreasing viral RNA level (HCV < 0.20 log copies /mL/month).

Sustained responses were 0/40 (0%) in group 1, 6/54 (11.1%) in group 2, and 25/47 (53.2%) in group 3 ($p < 0.0001$). Multivariate logistic regression analysis showed that reduction of HCV RNA level is an independent prediction factor for sustained response ($p < 0.0001$). A low viral load (< 2 million copies per milliliter; 800 IU/mL) is associ-

ated with a high probability of sustained viral response. The sustained viral response rate after 24 weeks of treatment is 1.5 times greater in patients with low viral loads than in patients with high viral loads. Martinot et al.¹⁸ analyzed data of 296 patients from four controlled studies and found that the sustained viral response to interferon treatment was 37%, 14%, and 6% in patients with low, intermediate, and high levels of pretreatment HCV RNA, respectively. Lee et al.^{21,23} found that a reduction in HCV RNA levels less than $2 \log_{10}$ in week 12 of treatment predicted an unsustained viral response (negative predictive value = 98%).

The Tokyo Chiba Hepatitis Research Group carried out a study (20) with 272 patients who had chronic hepatitis C but not cirrhosis and who were treated with 6 million or 9 million IU of interferon for 6 months. After treatment, viral RNA was undetectable in 75% of those treated with 9 million IU interferon and undetectable in 44% of those treated with 6 million IU interferon ($p < 0.05$). Patients with viral loads of 10^4 or 10^5 copies of HCV RNA per milliliter of blood had sustained responses of 52% and 19% respectively ($p = 0.029$). The virus eradication rate in patients with serotype 2 was higher than in those with serotype 1. In patients given 6 million IU interferon, virus eradication rates were 53% in those with serotype 2 vs 15% in those with serotype 1; in patients treated with 9 million IU interferon, virus eradication rates were 76% in those with serotype 2 vs 29% in those with serotype 1 ($p < 0.05$).

In the prospective study of Muto et al.,²¹ 66 patients were evaluated, 53 of whom complied with the treatment. A sustained virological response occurred in 21 patients (40%). HCV core antigen levels of 500 fmol/L or less, HCV RNA levels of 100 IU/mL or less, and a non-1b genotype were identified by univariate analysis as predictors of sustained virological response to treatment with interferon alfa. The early virological response was considered significant as HCV core antigen was undetectable in all responders one week after initiating interferon alfa treatment and was negative at the follow-up examination. HCV RNA was absent from the serum of all responders 4 weeks after the initiation of treatment and remained absent. Both markers were present in nonresponders. Patients with viral loads greater than 2,000,000 copies per milliliter or 800.000 IU/mL have the worst responses.

c. Genetic hypervariability

The role of quasispecies is controversial; some authors reported that the quasispecies rate decreased during the first 3 months of the infection in responders who recovered, remained stable in patients who developed low-grade chronic hepatitis, and increased in those who developed severe-to-advanced chronic hepatitis.^{27,28}

Complexity analysis of HCV quasispecies has been used to identify factors predictive of responses to antiviral treatment. It has been reported that patients with a low complexity of quasispecies in the hypervariable-1

region of the E2/NS1 gene region have a higher probability of responding to treatment. Therefore, the higher the number of HCV genomes in the serum, the higher the probability that a HCV strain will be resilient against immunological and antiviral repression. However, complexity analysis is unsuitable for application in clinical practices.^{24,25,29,30}

Determining the region of sensitivity to interferon

Within protein NS5A, a region of 40 amino acids called the interferon sensitivity-determining region (ISDR) is associated with responsiveness to treatment with interferon alfa.²⁶⁻³⁰ The HCV strain that is resistant to interferon alfa has the same sequence in the ISDR as genotype 1b. Patients with four or more amino acid substitutions in the ISDR (mutant type) exhibit full responses to treatment while those without substitutions (wild type) and 87% of those with 1–3 substitutions (intermediate type) do not respond to treatment. After treatment, the frequency of HCV quasiespecies with wild-type ISDR sequences increases, while that of quasiespecies with amino acid substitutions in the ISDR decreases. European studies have failed to replicate the results of many of these studies, most of which are of Japanese origin.³⁰ There are two possible reasons for this discrepancy: (1) the interferon dose used in European studies is half that used in Japanese studies, and (2) the incidence of patients with substitutions in the ISDR is 20% in Japan and 5% in Europe.

d. Coinfection with other viruses

Cacciola et al.³⁵ studied 200 patients, where 47% of patients did not respond to treatment with interferon having as well HBV-mDNA and this only occurred in 25% of responders. Therefore, the presence of markers of the hepatitis B virus in patients with chronic hepatitis C is interpreted by some as negative predictors of the response to treatment.^{32,33} Hepatitis C patients who are coinfecting with HIV tend to develop fibrosis faster, and it progresses earlier to liver failure and hepatocellular carcinoma. In contrast, HCV has no effect on the progression of HIV infection to AIDS. Therapy with interferon plus ribavirin results in sustained viral responses in 38% of patients with HCV genotype 1 and 73% of patients with HCV genotypes 2 or 3; therefore, it appears that HIV is not a predictive factor for HCV treatment response

2. Predictive factors associated with the host

The univariate analysis of Muto et al.²⁵ identified age as a predictor of response to treatment with interferon. Patients 50 years or more of age responded better to treatment in the presence of HLA (Antigen Histocompatibility Antigens) DR6 or DR52 and platelets levels of more than $14 \times 10^4/\text{mm}^3$.

Obesity and chronic hepatitis C

Obesity reduces the efficacy of treatment with interferon. Liver steatosis accelerates the progression of chronic hepatitis C, increasing the necroinflammatory component and the grade of fibrosis. Liver steatosis apparently confers resistance to antiviral treatment. Obesity is likely to affect the immune response through the induction of resistance to leptin. Steatosis is frequent in biopsies from HCV-infected patients and may be extensive and severe. In a study of more than 400 chronic hepatitis C patients, steatosis was detected in 65% and severe steatosis was detected in 23%. Patients infected with HCV genotype 3 had higher rates of steatosis and more severe grades of steatosis than those infected with HCV genotypes 1 or 2. Metabolic steatosis is common in patients with HCV genotypes 1 or 2. This type of steatosis is associated with nonalcoholic fatty liver, obesity, and type II diabetes. In patients with HCV genotype 3, steatosis seems to be related to the direct effect of viral proteins such as HCV core protein and NS5A, which interfere with cellular intake and transport of triglycerides. However, the cause of steatosis may also contribute to the progression of fibrosis in patients with HCV. In cases of obesity in which the body mass index is greater than 30 kg/m^2 , moderate or severe steatosis and type II diabetes are associated with advanced stages of the disease. These findings indicate that the extent of steatosis should be determined in patients with hepatitis C and that dietary and therapeutic strategies should be developed to prevent or reduce this problem in conjunction with antivirals.

Patton et al.⁴³ studied 574 patients with chronic hepatitis C and found that in cases of infection with HCV genotype 1, fibrosis was associated with the severity of steatosis ($p < 0.01$) and that patients who had a sustained virological response had a lower grade of pretreatment steatosis than nonresponders ($4.6 \pm 1.6\%$ vs $10.1 \pm 1.1\%$; $p = 0.02$). More HCV genotype 1 patients with early virological responses had grade 0 steatosis than those who did not have early responses (71% vs 42%; $p = 0.003$). It was concluded that steatosis is an important cofactor in chronic hepatitis C, is associated with fibrosis, and reduces the incidence of sustained virological responses in patients infected with genotype 1 HCV. Other predictors of treatment response associated with the host are sex (women respond better than men), body weight, and duration of infection.²²

The efficacy of treatment of 100 Black patients with pegylated interferon alfa 2b and ribavirin was studied in a trial carried out at 16 centers in the USA. The sustained virological response at week 48 was 20% in Black people vs 58% in Caucasians. This study also confirmed that early virological response is not a good indicator of treatment response in Blacks because only 48% of patients who had early virological responses

had sustained virological responses. Another study showed that Blacks have the worst response to treatment (21%), followed by Hispanics (27%), Caucasians (37%), and Asians (53%).

e. Analytic predictive factors

It has been shown that there is a positive correlation between baseline ALT levels and the probability of a response to treatment and that a baseline AST/ALT quotient of 0.5 or lower is predictive of a favorable response to treatment. Hepatic iron concentrations are greater in nonresponders. The amount of iron deposited in the mesenchymal cells of the portal spaces is predictive of a lack of response. The probability of responding to antiviral therapy is greater if less than 40% of portal tracts have deposits of iron. Up to 87% of nonresponders have elevated ferritin levels

f. Immunological predictive factors

Patients who respond to antiviral treatment have lower levels of tumor necrosis factor α and higher levels of interleukin-8. Levels of IL-2 are elevated after 4 weeks of treatment in nonresponders but not in responders. The presence of antinuclear antibodies in the baseline sample is predictive of a negative response. Other immunological markers such as anti-E1, anti-E2, and anti-NS5A, which have also been proposed as response predictors, do not have sufficient sensitivity to be useful in clinical practices.

A multivariate analysis of predictive factors in 100 patients studied by Vandelli et al.⁵¹ showed that baseline levels of core HCV IgM were significantly lower in patients who had full, sustained responses. Core anti HCV IgM levels greater than 3.8 times the cutoff value of the assay were associated with lack of response to treatment; undetectable core HCV IgM levels 6 months after termination of treatment were associated with full, sustained responses.

g. Histological predictive factors

Patients with hepatitis C and cirrhosis have low rates of sustained responses. Even when cirrhosis is absent, the probability of a response to treatment decreases as the degree of fibrosis increases. In other study it was defined as predictive factors to antiviral treatment, the patients without cirrhosis and without fibrosis in bridge, besides the Knodell index should be lower than 10.^{6,8,10}

h. Adherence to or compliance with treatment

It has been determined that patients who comply with the treatment in an amount higher than 80% with a duration of time higher than 80% better the sustained response, including the genotype 1.

In the International Hepatitis Interventional Therapy Group⁵² trial, 1,010 patients were treated with interferon α

2b plus ribavirin and 511 patients were treated with pegylated interferon α 2b (1.5 μ g/kg/week) plus ribavirin. The sustained virological response was 52% in patients treated with interferon α 2b plus ribavirin, and 63% in patients treated with pegylated interferon α 2b plus ribavirin, including genotype 1, in patients who received + than 80% of treatment and a duration > 80% in time.

Recommendations of the consensus panel

1. Which are the main predictive factors of a good response to treatment?
 - level of viral load
 - viral genotype
 - grade of fibrosis

The most important factor is viral genotype

The quality of evidence for this recommendation was given a rating of 1

Which is the main negative predictive factor of response during treatment?

Detectable viral load or a reduction of less than 2 log at week 12 of treatment (evidence quality = 1). However, obesity also has an effect on the response to treatment (evidence quality = 2).

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