Revisiting the Predictors of a Sustained Virologic Response in the Era of Direct-Acting Antiviral Therapy for Hepatitis C Virus

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Several host (age, sex, race, fibrosis stage, interleukin 28B polymorphism) and viral factors (hepatitis C virus [HCV] genotype, viral load) allow estimating the response to interferon-based therapies (which includes first-generation protease inhibitors) before treatment. However, treatment should not be denied to any patient based on unfavorable factors alone. Metabolic conditions associated with poor response (diabetes, insulin resistance, obesity) and alcohol abuse can be influenced before starting treatment. “On-treatment” predictors of response allow treatment to be tailored to the individual need of the patient. Patients with undetectable HCV RNA after 4 weeks (rapid virologic response [RVR]) have the highest chance for cure (>85%) both by dual and triple therapy. For triple therapy, the decision to shorten treatment requires that the virus remains undetectable for an additional 8 (telaprevir) to 20 (boceprevir) weeks (extended RVR). Based on viral kinetics, an even earlier prediction after 2 weeks of treatment with direct acting antivirals appears feasible.

Keywords. hepatitis C; peginterferon; ribavirin; direct acting antivirals; prediction.

Predicting response reduces therapy empiricism and costs, while optimizing treatment outcomes. For patients with chronic hepatitis C there are 2 types of predictors: factors that are obtained before treatment (baseline predictors) and measurement of viral load on treatment (on treatment predictors). The use of baseline predictors is to select the most appropriate treatment for a given patient (ie, choice of drug) and of on treatment predictors to adapt treatment to the actual need of patients (ie, response-guided therapy). The predictive power of baseline predictors is not accurate enough to deny treatment in a patient with many unfavorable factors.

Pretreatment Prediction
Host Factors
Several host factors affect outcome [1, 2]. Among patients in the United States, treatment success is lower in African Americans than in white individuals [3, 4], possibly due to a higher frequency of interleukin 28B (IL-28B) T-allele carriers [5] or lower vitamin D levels [6]. There are no data on European patients of African origin. In contrast, Asian patients have much higher sustained virologic response (SVR) rates [7]. Response rates to pegylated interferon/ribavirin (peg-IFN/RBV) or triple therapy are lower in patients, both in treatment-naive [8, 9] and in treatment-experienced patients [10, 11] with advanced liver fibrosis [12]. Among cirrhotic patients with marked portal hypertension (hepatic venous pressure gradient ≥10 mm Hg), SVR rates were lower compared to those without (16% vs 48%, respectively) [13]. Similar data are not available for patients receiving triple therapy.

Patients with ethanol abuse and metabolic disorders, including overweight, diabetes, and insulin resistance (IR), have an impaired response to peg-IFN/RBV.
IR appears to be less important for triple therapy with direct-acting antivirals (DAAs). Within 14 days of treatment with the protease inhibitor (PI) danoprevir, IR improved with most patients achieving normal Homeostasis Model Assessment (HOMA) values [17]. In a phase 2 trial investigating different dosing schedules for telaprevir-based triple therapy, hepatitis C virus (HCV) genotype 1–infected treatment-naive patients [18], baseline HOMA-IR was not predictive of response to treatment [19]. After treatment, HOMA-IR became significantly lower in patients who achieved an SVR than in those who did not. In multivariate analyses, only low fibrosis stage and high low-density lipoprotein cholesterol level were predictive of SVR. Besides metabolic disorders, HCV itself may promote IR [20]. Successful therapy results in improvements in IR, and decreases the risk of diabetes [21].

Genetics

A genome-wide association study [22] identified the single-nucleotide polymorphism rs12979860 in the IL-28B region associated with SVR [5]. The favorable CC genotype is predictive of both treatment-induced clearance [23, 24] during chronic infection and spontaneous clearance in acute infection [25].

The impact of the IL-8 polymorphism in patients receiving triple therapy is conflicting [26]. Because treatment with DAAs is given in combination with both peg-IFN and RBV IL-28B, polymorphism should have the same (or similar) predictive role as in dual therapy. In fact, C/C carriers had the best outcome in studies with boceprevir [27], faldaprevir [28], simeprevir [29], and telaprevir [30]. Whether patients with the favorable CC genotype may have a shorter therapy without compromising SVR rates is currently under evaluation.

A clear effect of IL-28 on treatment outcome was documented in our patients participating in DAA trials [31]. Although experience is limited in patients receiving interferon-free treatment, IL-28B genotype appears to affect success rates [26, 32, 33]. In the INFORM-1 trial (danoprevir + mercicatine), viral load decline was slightly faster in IL-28B CC patients [32]. In the SOUND 2 trial (danoprevir + BI 207127) [33], all IL-28B C/C genotype 1b (GT1b) patients achieved SVR, whereas the outcome of GT1a patients was substantially worse. These observations suggest that some endogenous interferon is needed for effective viral clearance [34], protecting against the emergence of viral mutants, at least in patients with genotypes 2 and 3, 24 weeks of dual therapy with a fixed dose of ribavirin is sufficient [35]. A further analysis in 1744 interferon-naive study participants identified 5 independent characteristics associated with SVR: genotype 2 or 3; baseline interferon viral load <3.5 million copies/mL; no portal fibrosis; female sex; and age <40 years [36]. Recent studies found in treatment schedules containing a DAA that GT1b patients had fewer relapses and breakthroughs than did GT1a patients [33, 37, 38].

VIRAL KINETIC STUDIES

Viral Kinetic Studies With Peg-IFN/RBV

Serum HCV levels on peg-IFN/RBV show a biphasic decline [39] starting 8–9 hours after the first interferon dose and reaching the nadir after 24 hours. A slower second phase occurs between 2 and 14 days of initiation of treatment and has a half-life of 1.7 to 70 days. The first phase is a dose-dependent direct effect on HCV production or release, while the second phase reflects the overall death rate of HCV-infected hepatocytes [40]. Because interferon is able to block infection of noninfected hepatocytes, the pool of infected hepatocytes declines over time due to elimination by specific cytotoxic T lymphocytes response or apoptosis.

Viral Kinetic Studies With DAA

The second-phase slope of viral decline by telaprevir strongly correlated with treatment effectiveness and was about 4-fold more rapid than with interferon-based therapies [41]. On the basis of this result, it was suggested that in 95% of fully compliant patients the last virus particle should be eliminated by week 7 of therapy. If the remaining infected hepatocytes act as a potential reservoir for the renewal of infection, no more than 10 weeks of treatment should be sufficient to clear the infection. Ten weeks of treatment with telaprevir is not possible for all patients. In the ADVANCE trial [8], patients who received 8–12 weeks of telaprevir-containing triple therapy followed by 12 weeks of dual therapy still only achieved SVR rates of 69%–75%. Thus, just 10 weeks of therapy, as predicted by Guedj et al [41], appears insufficient to achieve viral clearance in the clinic.

TREATMENT PREDICTION

Successful treatment of chronic hepatitis C requires 3 independent events to occur: (1) the virus must be sensitive to peg-IFN and to the DAA chosen; (2) all infected hepatocytes must be eliminated; and (3) patients must comply with the treatment regimens. Resistance-associated variants (RAVs) may be present at baseline in low quantities and will emerge on treatment in the presence of an interferon-insensitive virus [42].
This may constitute a problem if DAAs with a low genetic barrier are used. Currently, pretreatment testing for RAVs is not recommended.

### TIME COURSE OF VIRAL RESPONSE

The decline in viral load as early as 24 hours after the initial interferon dose predicts treatment outcome [43]. In general, the faster the initial viral decline, the higher are the chances to obtain an SVR [44]. Patients clearing the virus within 4 weeks (rapid virologic response [RVR]) have the highest rate of SVR [44], independent of viral genotype [45] or IL-28B polymorphism [46], and have the option to shorten treatment [47, 48]. The proportion of patients achieving RVR increased with the addition of a PI (from 20%–25% to 66%–68%). The trials with boceprevir [9] had a 4-week lead in phase with peg-IFN/RBV allowing incorporating the prediction algorithms of dual therapy. Compared with dual therapy alone, patients with RVR may not benefit from the addition of boceprevir, whereas partial lead-in phase responders had improved SVR rates on triple therapy. In contrast, 51% of null responders developed RAVs. These observations highlight the importance of rapid viral suppression.

For triple therapy instead of RVR, the term “extended RVR” (eRVR) is used to account for late viral breakthroughs or the emergence of PI-resistant viral strains. The definitions differ with the drug used [49]. Patients with eRVR had the highest SVR rates even if treatment was shortened to 24 weeks (telaprevir) or 28 (boceprevir) weeks. Because the positive predictive value of HCV RNA levels at week 2 in patients in trials with various PIs is equal to that at week 4 (Table 1), an earlier decision for response-guided therapy may be feasible.

As for all antiviral therapies, adherence with treatment is a key to success. The 80/80/80 rule (eg, taking 80% of peg-IFN, 80% of RBV, 80% of the time) with dual therapy [50] may have been more forgiving compared with adherence with HCV PIs, where minor declines of adherence may trigger the emergence of RAVs.

### CONCLUSIONS

Both baseline and on-treatment predictors are important to estimate the likelihood of cure by peg-IFN/RBV in patients with chronic hepatitis C. As long as interferon is part of the treatment, all predictors will remain valid, but must be adapted to account for the faster viral declined induced by DAAs.

### Note

**Potential conflicts of interest.** P. F. is a member of the global advisory board and of the speaker’s bureaus of Roche and Rottapharm-Madaus, and is also an advisor to Boehringer Ingelheim, Vertex/Tibotec, Novartis, GlaxoSmithKline, and Merck Sharpe & Dohme (MSD). P. F. also receives an unrestricted research grant from Roche Austria and MSD Austria. All other authors report no potential conflicts.

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### References


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**Table 1. Viral Response at Various Time Points to Predict Sustained Virologic Response in Treatment-Naive Patients Receiving Triple Therapy**

<table>
<thead>
<tr>
<th></th>
<th>HCV-RNA Week 1</th>
<th>HCV-RNA Week 2</th>
<th>HCV-RNA Week 4</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>&lt;LOD &lt;100 IU/mL</td>
<td>&lt;LOD &lt;100 IU/mL</td>
<td>&lt;LOD &lt;100 IU/mL</td>
</tr>
<tr>
<td>PPV</td>
<td>1 0.926</td>
<td>0.892 0.849</td>
<td>0.885 0.87</td>
</tr>
<tr>
<td>NPV</td>
<td>0.761 0.36</td>
<td>0.583 0.75</td>
<td>0.889 1</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.353 0.61</td>
<td>0.778 0.957</td>
<td>0.979 1</td>
</tr>
<tr>
<td>Specificity</td>
<td>1 0.818</td>
<td>0.767 0.429</td>
<td>0.571 0.364</td>
</tr>
<tr>
<td>% with SVRa</td>
<td>11.5 51.9</td>
<td>89.2 84.9</td>
<td>88.5 82.5</td>
</tr>
</tbody>
</table>

Abbreviations: HCV, hepatitis C virus; LOD, level of detection; NPV, negative predictive value; PPV, positive predictive value; SVR, sustained virologic response.

*a Patients (n = 95) participated in studies with telaprevir (including also patients treated off study after the drug became available), simeprevir, danoprevir, and faldaprevir.

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