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

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.
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-naïve 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 + mericitabine), viral load decline was slightly faster in IL-28B CC patients [32]. In the SOUND 2 trial (faldaprevir + 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-naïve study participants identified 5 independent characteristics associated with SVR: genotype 2 or 3; baseline 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 dual 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 regimen. 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].
The decline in viral load as early as 24 hours after the start of therapy is a key to success. The 80/80/80 rule (e.g., 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 decline induced by DAAs.

**Note**

Potential conflicts of interest. P. F. is a member of the global advisory board 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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