Genetic Variation in \textit{IL28B}: Impact on Drug Development for Chronic Hepatitis C Infection

PJ Clark\textsuperscript{1}, AJV Thompson\textsuperscript{1} and JG McHutchison\textsuperscript{1}

As more pharmacogenomic insights into diseases and their treatments and toxicities are published each year, the challenge arises to incorporate such insights into clinical practice and drug development.\textsuperscript{1} For instance, recent genomic discoveries related to hepatitis C offer a challenge to clinicians, researchers, and health administrators to translate this information into knowledge in order to develop safer and more effective therapeutic strategies for all patients.

INTERFERON-\(\lambda\), \textit{IL28B} GENETIC POLYMORPHISM, AND HCV INFECTION

Five recent genetic association studies have conclusively identified single-nucleotide polymorphisms (SNPs) close to the \textit{IL28B} gene region as the strongest pretreatment predictor of response (sustained viral response (SVR), no detectable virus 24 weeks after the end of treatment) to pegylated interferon-\(\alpha\) (IFN-\(\alpha\)) and ribavirin (pegIFN/RBV) therapy for patients with genotype-1 chronic hepatitis C virus (HCV).\textsuperscript{2–6} These same \textit{IL28B} polymorphisms are also strongly associated with spontaneous clearance of the virus after acute HCV infection.\textsuperscript{5,7} The \textit{IL28B} polymorphism influences viral kinetics and is associated with an early decline in viral load with treatment.\textsuperscript{8,9} Two SNPs (rs12979860 and rs8099917) in linkage disequilibrium have consistently provided the strongest signals and are likely to share a haplotype with the causal variant that has yet to be identified.

An important finding from these studies is that the genotype associated with a good response to treatment (C/C for SNP rs12979860) is less frequent in African Americans. To a large extent, these differences explain the poorer clinical response rates observed in African-American patients.\textsuperscript{2} Conversely, the favorable C/C genotype is more frequent in Asian populations, corresponding to the higher efficacy rates that have been observed in this group.\textsuperscript{10} However, the frequency of the \textit{IL28B} allele does not entirely explain heterogeneity in treatment response between racial groups. African Americans have lower SVR rates as compared with Caucasians even when matched across each \textit{IL28B} genotype.\textsuperscript{2} Despite very high frequencies of the allele in Asians, clinical trials in Asian patients have not universally demonstrated high SVR rates. Although \textit{IL28B} polymorphism has been one of the most significant steps toward advances in understanding differences in response, other host and viral factors remain important.

The mechanism through which \textit{IL28B} variation causes IFN sensitivity remains unclear. The SNPs thought to be most closely associated with the mechanism lie upstream of the \textit{IL28B} gene, and it is possible that they effect \textit{IL28B} transcription. Ge et al. observed no relationship between \textit{IL28B} mRNA levels and \textit{IL28B} polymorphism in peripheral blood mononuclear cells from non-HCV-infected volunteers in the SNPExpress database.\textsuperscript{2} However, Tanaka et al. observed that lower levels of \textit{IL28B} mRNA were associated with the poor-responder rs80999917 genotypes in peripheral blood mononuclear cells in a small group of HCV-infected patients.\textsuperscript{3} Suppiah et al. found lower constitutive expression of \textit{IL28A} and \textit{IL28B} in peripheral blood mononuclear cells from healthy controls carrying the rs80999917 poor-responder allele (\(P = 0.044\)). The data on gene expression are therefore conflicting. Several other potentially functional SNPs have been identified as being highly linked to the discovery SNPs, including the nonsynonymous SNP (rs8103142, Lys70Arg) in exon 2 of the \textit{IL28B} gene.\textsuperscript{2} This polymorphism potentially affects protein function, including receptor binding and protein stability.

The IFN-\(\lambda\) family or type III IFNs include \textit{IL28A}, \textit{IL28B}, and \textit{IL29}. IFN-\(\lambda\) shares many functional characteristics (e.g., downstream signal transduction) with type I IFN but has a more restricted receptor (IFN-\(\lambda\)-R) distribution, and it is expressed at high levels in hepatocytes but not in hemopoietic cells. IFN-\(\lambda\) has a direct antiviral effect on HCV that is additive with that of type 1 IFN.\textsuperscript{5,11–17} Teleologically, IFN-\(\lambda\) may have evolved to provide a more tissue-specific IFN response.\textsuperscript{14} The \textit{IL28B} discovery opens up new pathways to understand pathogenesis and develop therapies, not only in the treatment of hepatitis C–related liver disease, but for other chronic viral infections and immune-related injury in other organ systems.

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For chronic hepatitis C, an ideal treatment must be efficacious, simple, safe, and well tolerated, and also of short duration and cost-effective. It is critical to develop a better understanding of how recent findings related to host IL28B genotype will interact and potentially influence drug discovery and development. In this context, some relevant questions arise.

**Can the Duration of PegIFN/RBV Therapy Be Shortened on the Basis of IL28B Genotype?**

Host IL28B polymorphism allows identification of ~40% of genotype-1 HCV-infected Caucasians who have a 70–80% chance of SVR with current standard-of-care treatment, which consists of 48 weeks of pegIFN plus RBV. A commercial test is now available to guide clinicians and patients in the treatment decision-making process. We are of the opinion that knowledge of the effect of host IL28B genotype, in conjunction with viral kinetics during treatment, will be useful in helping to individualize drug regimens and treatment durations while preserving SVR rates (Figures 1 and 2).

Numerous prospective studies have found that patients infected with HCV genotype-1 and who achieve rapid viral response (RVR, viral negativity after 4 weeks of pegIFN/RBV) subsequently have a high rate of SVR after receiving only 24 weeks of pegIFN/RBV.18–20 It is likely that this “responder” group is enriched with patients who carry the favorable IL28B C/C alleles,8 and that 24 weeks of treatment may be sufficient to maintain high SVR rates (Figure 1). Theoretically, even a shorter duration (perhaps 12 weeks) may be possible in the future, using combination therapies with directly acting antivirals (DAAVs).

In poor response IL28B genotype patients (Figure 2), for whom current standard-of-care therapy provides only a 20–30% chance of a cure, strategies to improve efficacy will remain a major focus. Extending pegIFN/RBV therapy beyond 48 weeks has generally proved to be disappointing.16,17 Improved efficacy will therefore be achieved by the introduction of DAAVs and other novel agents working through alternative mechanisms of action (e.g., cyclophilin inhibitors). As shown conceptually (Figures 1 and 2), DAAVs may permit a shorter duration of therapy in certain patients, whereas more aggressive strategies with quadruple or alternative regimens may be necessary for others.

**How Will IL28B and DAAVs Interact and Fit into Future Hepatitis C Treatments?**

DAAVs inhibit HCV replication by specifically targeting viral enzymes such as nonstructural (NS) 3 protease and NS5A protease. Agents such as the NS3 protease inhibitors telaprevir and boceprevir will likely soon be approved.21,22 Phase II randomized clinical trials with these agents and 24–48 weeks of...
pegIFN/RBV demonstrate overall SVR rates of 67–74%, suggesting that DAAVs may overcome the effect of a “poor-response” IL28B genotype to some extent.\(^{21,23}\) Subgroup analyses demonstrated the benefit of adding DAAVs for patients with other “difficult-to-treat” characteristics and showed excellent response rates in patients who had previously failed treatment.\(^{24,25}\) Recently, a small study of a heterogeneous Japanese cohort suggested that the IL28B polymorphisms remain a critical pre-treatment predictor of response to telaprevir-based treatment.\(^{26}\) Therefore, careful analysis of the interaction of IL28B type and responses in different groups of patients who have been exposed to these novel protease inhibitors is the critical next step.

**Genotype-1 patients** who are homozygous for the IL28B good-responder allele have observed SVR rates of 70–80% on standard pegIFN/RBV. Two phase II trials of telaprevir—one in the United States and the other in Europe—compared standard-of-care therapy to 12 weeks of telaprevir combined with three different treatment arms of 12, 24, or 48 weeks of pegIFN/RBV.\(^{18–27}\) SVR rates were similar (67% vs. 61%) when duration was decreased from 48 to 24 weeks. Interestingly, in the European study’s 12-week arm, 60% of the patients (49 of 82) achieved SVR.\(^{27}\) This suggests that 12 weeks of therapy may be feasible with a three-drug regimen for selected patients (the corresponding arm in the US study had only 17 patients, with an SVR rate of 35%). For these patients, DAAVs may be included not with the primary objective of increasing SVR rates but with the aim of reducing treatment duration (Figure 1). Whenever possible, we also need to revisit such large clinical trials and, with informed consent of the subjects, collect DNA to reevaluate the results in different treatment arms in the light of the IL28B genotype. Prospective studies stratified for host IL28B genotype are needed in order to definitively identify patients in whom DAAV-containing shorter treatment regimens may be equally effective.

The IL28B polymorphism is associated with a decline in viral load in the first 12 weeks of therapy.\(^{8,9}\) How this knowledge will interact with the introduction of DAAVs will become evident in time. It may be relevant to the risk of drug resistance. Poor-response non-C/C host IL28B genotypes, possibly associated with slower viral suppression, may be at higher risk for the emergence of resistant variants and subsequent viral breakthrough. The scene is therefore set to diversify HCV treatment regimens with multiple new classes of potent DAAVs, drug combinations, and durations based, in part, on host IL28B genotype. The specific details will unfold as more data become available in the next 2 years. Shorter, highly potent multidrug regimens may provide the optimal “cocktail” for patients with good-response IL28B genotypes. Patients with poor-response IL28B genotypes will likely be tied to longer-duration courses of pegIFN/RBV combined with the newer agents (Figure 2). Economic modeling and formal, independent cost-effectiveness analyses will clearly be important to evaluate the relative costs and benefits of these varied strategies.

### IS THERE A GROUP OF PATIENTS WHO MAY BE CURED WITHOUT IFN?

PegIFN and RBV are likely to remain the backbone of HCV therapy for the foreseeable future. The addition of a DAAV does not permit the exclusion of RBV without compromising RVR rates, viral breakthrough, SVR, and relapse rates.\(^{27}\)

The limited data available on combination DAAV therapy without IFN and RBV suggest that there is potent additive antiviral action and that the oral combination regimens are well tolerated.\(^{28}\) Five such exploratory “all-oral” trials are under way, but most will receive these DAAV combinations for a short period of time and then start pegIFN/RBV. Such trials might be most appropriate initially in patients with the responder C/C IL28B genotype, given that patients who fail an exploratory all-oral regimen could be “rescued” with pegIFN/RBV, safe in the knowledge that they have an excellent chance of cure. If, on the other hand, the virus can no longer be detected after stopping such oral regimens, it provides a basis to assess efficacy and cure rates with such strategies. This would be a major milestone denoting progress in the field. Finally, such “game-changing” regimens might need to include two, three, or four oral antivirals, acting at different targets so as to increase the likelihood of success in different populations of patients. IL28B profiling and a broader understanding of the “biosignatures” predictive of cure with all-oral drug regimens will be a priority.

### WHAT ARE THE IMPLICATIONS FOR RESEARCH IN THIS FIELD?

A knowledge of host IL28B genotype opens exciting new areas of basic research and clinical inquiry (Table 1). There is an

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Table 1 Important research priorities related to IL28B host genotype

<table>
<thead>
<tr>
<th>Basic research priorities</th>
<th>Next important clinical studies(^a)</th>
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<tbody>
<tr>
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**Important research priorities related to** IL28B **host genotype**

**Basic research priorities**

- To identify the causal variant and its biological functionality
- To pursue novel drug design and development strategies based on these pathways and targets
- To characterize the biosignatures of response to different treatment regimens (e.g., with 2, 3, and 4 drugs)

**Next important clinical studies\(^a\)**

- Prospective: 24 vs. 48 weeks of pegIFN and RBV therapy for IL28B C/C genotype, treatment-naive patients infected with HCV genotype 1
- Prospective: reduced-duration, triple-drug regimens for treatment-naïve patients with favorable IL28B C/C genotype
- Prospective: novel immunomodulator therapies and their interaction with host IL28B genotype
- Prospective: all-oral DAAV regimens for patients with favorable IL28B C/C genotypes in small trials, followed by a period of observation. If such regimens fail, these patients can be effectively rescued with pegIFN and RBV
- Retrospective: evaluation of the interaction of IL28B genotype with treatment response in well-characterized cohorts of patients currently in phase I–III protease and polymerase inhibitor trials.
- Determine frequencies of IL28B polymorphisms in different populations globally

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important need for basic research to improve our understanding of the fundamental biology and clinical observations related to IL28B polymorphisms and how these polymorphisms are related to IFN-λ and other IFNs to affect innate and cell-mediated immunity.\textsuperscript{12,13,15,17} Identifying the causal variant and characterizing its effect on gene function and expression may provide new biological insights of therapeutic relevance.

An obvious implication for researchers is the development of more refined and targeted IFN therapies. Because of its more restricted receptor distribution, specific targeting of the IFN-λ-R may avoid some of the systemic side effects associated with pegIFN/RBV therapy. A phase I trial of IFN-λ-1 (IL29) has recently demonstrated potent antiviral activity, with reduced systemic side effects in patients with genotype-1 chronic hepatitis C.\textsuperscript{29}

There is a clear need for prospective clinical research trials to understand how existing agents (pegIFN/RBV) and future strategies will integrate with host IL28B genotype. The goal will be to optimize efficacy, patient convenience, and safety. The IL28B genotype now has major implications for HCV research protocol design in terms of stratification of trials involving novel agents and treatment strategies. This will be particularly important for smaller conceptual studies, for which ascertainment bias may have a significant impact on the interpretation of results.

**CONCLUSION**

Knowledge related to host IL28B genotype has altered the HCV treatment landscape from a clinical and research perspective. Effective translation of this emerging knowledge will require engagement on the part of patients, clinicians, researchers, health administrators, and the pharmaceutical industry. The outcome, we hope, will be shorter, more efficacious, and better tolerated treatments for patients, with individualized strategies based on the host genotype. All would benefit in such a system.

**ACKNOWLEDGMENTS**

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**CONFLICT OF INTEREST**

J.G.M. has received research and grant support from Schering-Plough, Merck, and Roche. J.G.M. has received consulting fees and acted in an advisory capacity for Schering-Plough and Merck. J.G.M. and A.J.V.T. are co-inventors of a patent application based on the IL28B discovery. P.J.C. declared no conflict of interest.

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