Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for *IFNL3* (*IL28B*) Genotype and PEG Interferon-α–Based Regimens

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Pegylated interferon-α (PEG-IFN-α or PEG-IFN 2a and 2b)– and ribavirin (RBV)-based regimens are the mainstay for treatment of hepatitis C virus (HCV) genotype 1. *IFNL3* (*IL28B*) genotype is the strongest baseline predictor of response to PEG-IFN-α and RBV therapy in previously untreated patients and can be used by patients and clinicians as part of the shared decision-making process for initiating treatment for HCV infection. We provide information regarding the clinical use of PEG-IFN-α- and RBV-containing regimens based on *IFNL3* genotype.

The purpose of this guideline is to provide information regarding the clinical use of *IFNL3* (***IL28B***) genotyping to guide the use of pegylated interferon-α (PEG-IFN-α or PEG-IFN 2a and 2b) and ribavirin (RBV) combination therapy, including treatment with direct-acting antivirals approved for hepatitis C virus (HCV) genotype 1 infection. Demographic and other clinical variables, such as adherence to psychological or pharmacological therapy, concomitant use of other drugs that may influence efficacy of antiviral treatment, or patient-specific disease characteristics, are not the focus of this guideline. The Clinical Pharmacogenetics Implementation Consortium develops peer-reviewed guidelines that are published and updated regularly at http://www.pharmgkb.org on the basis of emerging evidence.

FOCUSED LITERATURE REVIEW

A systematic literature review focused on *IFNL3* (*IL28B*) genotype and PEG-IFN-α use was conducted (see **Supplementary Material** online). This guideline was developed on the basis of interpretation of the literature by the authors and experts in the field.

DRUGS: PEG-IFN-α

Background

Infection with HCV affects >150 million people worldwide and is one of the leading causes of cirrhosis and hepatocellular carcinoma (hepatitis C fact sheet, Geneva, Switzerland: World Health Organization; accessed 30 September 2012 at http://www.who.int/mediacentre/factsheets/fs164/en/index.html). Before 2011, treatment for chronic HCV infection consisted of combination PEG-IFN-α and RBV therapy for 24 weeks for HCV genotypes 2 and 3 and for 48 weeks for other HCV genotypes.[1] In 2011, two first-generation HCV protease inhibitors, boceprevir and telaprevir, were approved to treat HCV genotype 1 infection in many countries, including the United States and the countries of the European Union. These direct-acting antiviral agents are indicated in combination with PEG-IFN-α and RBV therapy for patients with HCV genotype 1 infection, and this regimen is preferred over PEG-IFN-α and RBV alone in countries where direct-acting antivirals have been approved.

The primary goal of treatment is eradication of HCV as measured by sustained virologic response (SVR, defined by undetectable serum viral RNA 12–24 weeks after the end of treatment), which equates with cure of the infection and leads to lower morbidity and mortality.[2] However, combination therapy for HCV treatment has a number of limitations. The treatment is expensive, is associated with many side effects, and lasts 24–48 weeks. SVR rates are low for patients with HCV genotypes 1 and 4 treated with PEG-IFN-α and RBV combination.[3] The addition of the first-generation protease inhibitors to PEG-IFN-α and RBV has led to SVR rates of 69–75% for patients with HCV genotype 1 infection naive to HCV treatment, but SVR rates are lower for patients who failed previous treatment with PEG-IFN-α and RBV. The SVR rate varies drastically among different

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races and ethnicities, with patients of African ancestry having much lower response rates as compared with Caucasians and Asians, supporting genetic predisposition to response.[4,5] Both host and viral factors have been previously reported to be associated with SVR. Predictors of SVR include HCV genotypes 2 and 3, lower baseline serum HCV RNA level, younger age, female sex, lower hepatic fibrosis stage, lack of insulin resistance, and lower body mass index.[3]

GENE: *IFNL3*

Background

IFNL3, also known as *IL28B*, encodes interferon-λ 3 (IFN-λ 3), a member of the type 3 IFN-λ family with antiviral, antiproliferative, and immune-modulatory activities.[6] IFN-λs can be induced by viruses and inhibit HCV replication *in vitro*.[6] Similar to type 1 interferons (IFN-αs), IFN-λs signal through the common janus kinase–signal transducer and activator of transcription and mitogen-activated protein kinase pathways and induce IFN-stimulated gene expression.[6] However, IFN-λs engage a unique heterodimeric receptor complex, which is composed of the IL-10R2 (*IL10RB* gene) and IFN-λR1 (*IL28RA* gene) receptor chains,[6] and are highly expressed only in hepatocytes and epithelial cells, distinct from the ubiquitously expressed IFN-α receptor.

IFNL3 variation is the strongest established pretreatment predictor of treatment response for previously untreated (naive) patients with HCV genotype 1 (see **Supplementary Table S1** online for additional genes associated with HCV treatment response). Four genome-wide association studies have independently associated *IFNL3* genetic variation with treatment-induced clearance of HCV following PEG-IFN-α and RBV therapy,[7–10] which was later validated in candidate gene studies.[11–13] These variants are located on chromosome 19, near the *IFNL3* gene. The two most commonly tested single -nucleotide polymorphisms are rs12979860 and rs8099917, which are in close proximity and in strong linkage disequilibrium. Favorable response *IFNL3* genotypes (CC for rs12979860 and TT for rs8099917) are associated with an approximate two-fold increase in SVR for HCV genotype 1 patients. However, rs12979860 has been found to be less reliable for predicting response to PEG-IFN-α and RBV therapy in Japanese patients as compared with rs8099917.[14] The rs12979860 allele frequency varies among different ethnic groups (**Supplementary Tables S2 and S3** online), and largely explains the differences in treatment response rates among East Asians, Caucasians, African Americans, and Hispanics with chronic HCV infection.[10,15] The rs12979860 favorable C allele is most frequently present in East Asians (allele frequency nearly 0.9), followed by Caucasians and Hispanics, and is the least common among individuals of African origin (allele frequencies of 0.63, 0.55, and 0.39, respectively).[10,16,17]

The mechanisms by which *IFNL3* variations affect antiviral response are still poorly understood. Many of the *IFNL3* variants associated with PEG-IFN-α and RBV treatment outcomes are not within the coding region but only in close proximity to the *IFNL3* gene. The effects of this variation on *IFNL3* gene expression or intrahepatic IFN-stimulated gene expression remain controversial,[8,10,18–20] and the impact on protein stability or receptor-binding potency of these variants has not been reported. Recently, multiple studies demonstrated that the favorable rs12979860 genotype may affect treatment outcomes via improved innate immune response to IFN therapy and more rapid viral kinetics independent of IFN-stimulated gene expression.[21–24] This variant is also associated with better early viral kinetics during IFN-free treatment of patients with chronic hepatitis C.[25]

Genetic test interpretation

Laboratory results for *IFNL3* genotype are typically reported as reference single-nucleotide polymorphism identification number (rs) followed by the specific genotype (i.e., rs12979860 CC, CT, or TT) with accompanying interpretation (i.e., favorable genotype vs. unfavorable genotype). The assignment of the likely IFNL3 phenotype, based on diplotypes, is summarized in **Table 1**.

Available genetic test options

See the **Supplementary Material** online and http://www.PharmGKB.org for more information on commercially available clinical testing options.

Linking genetic variability to variability in drug-related phenotypes

There is substantial evidence linking *IFNL3* genotype to phenotypic variability (see **Supplementary Table S4** online). Among patients treated for chronic HCV infection, *IFNL3* genotype is associated with early viral kinetics and improved SVR. As early as week 4 of therapy, patients with the favorable *IFNL3* genotype are more likely to have undetectable HCV RNA.

Table 1 Assignment of probable IFNL3 phenotypes based on genotypes

			Genotype
Observed phenotype	Description	Genotype definitions	rs12979860
Favorable response genotype	Increased likelihood of response (higher SVR rate) to PEG-IFN-α and RBV therapy as compared with patients with unfavorable response genotype	An individual carrying two favorable response alleles	CC
Unfavorable response genotype	Decreased likelihood of response (lower SVR rate) to PEG-IFN-α and RBV therapy as compared with patients with favorable response genotype	An individual carrying at least one unfavorable response allele	CT or TT

PEG-IFN-α, pegylated interferon-α 2a or 2b; RBV, ribavirin; SVR, sustained virologic response.

Application of a grading system to the evidence linking genotypic to phenotypic variability indicates a high quality of evidence in the majority of cases (**Supplementary Table S4** online). This body of evidence provides the basis for the therapy recommendations in **Table 2**.

Therapeutic recommendations

Table 2 summarizes the therapeutic recommendations for PEG-IFN-α and RBV therapy based on *IFNL3* genotype. Treatment of HCV genotype 1 infection varies throughout the world currently because some regions have access to the new direct-acting antivirals in combination with PEG-IFN-α and RBV, whereas other regions have access only to PEG-IFN-α and RBV. The role of *IFNL3* genotyping depends on treatment selection. *IFNL3* genotype is only one factor that can influence response rates to PEG-IFN-α and RBV therapy in HCV genotype 1 infection and should be interpreted in the context of other clinical and genetic factors.

PEG-IFN-α and RBV. For patients treated with PEG-IFN-α and RBV alone, *IFNL3* genotype is the strongest pretreatment predictor of HCV treatment response. In the intention-to-treat analysis of the original discovery cohort with rs12979860, Caucasian patients with CC genotype were more likely than those with CT or TT genotype to have undetectable serum viral RNA by week 4 (28 vs. 5 and 5%, respectively; $P < 0.0001$) and to achieve SVR (69 vs. 33 and 27%, respectively; $P < 0.0001$).[17] Similar patterns were observed in Hispanic and African-American patients in this cohort. HCV treatment is associated with significant side effects, and the likelihood of response treatment influences shared decision making between clinicians and patients about initiating treatment.

Protease inhibitor combination regimens—treatment naive. For treatment-naive patients with genotype 1 infection who are treated with protease inhibitor combinations, all *IFNL3* genotypes have improved response rates as compared with patients treated with PEG-IFN-α and RBV only. However, patients with the favorable *IFNL3* genotype still have higher response rates with the protease inhibitor combination in treatment-naive patients, and these response rates may guide patients and clinicians in their treatment decisions. In the boceprevir phase III treatment naive study of combination with PEG-IFN-α and RBV, SVR rates for rs12979860 CC patients receiving boceprevir ranged from 80 to 82% as compared with 65–71% for CT patients and 59–65% for TT patients.[26] Moreover, multivariate regression analysis revealed that rs12979860 CC genotype was a predictor of SVR as compared with CT (odds ratio = 2.6, 95% confidence interval = 1.3–5.1) and TT genotypes (odds ratio = 2.1, 95% confidence interval = 1.2–3.7).

Role of the lead-in. Although *IFNL3* genotype is the strongest pretreatment predictor of response to IFN-α-based therapy, the use of the early on-treatment antiviral response has also been extensively evaluated.[27] The *IFNL3* genotype is a marker for IFN responsiveness, and patients with the favorable *IFNL3* genotype are more likely to have significant reductions in HCV RNA during the first 4 weeks of therapy. The boceprevir combination regimen starts with 4 weeks of PEG-IFN-α and RBV, and boceprevir is added in the fifth week. In the analysis of the boceprevir phase III studies, SVR models that considered only baseline characteristics found that the *IFNL3* genotype was a predictor of SVR.[26,27] When the lead-in response was added to these models, the *IFNL3* genotype was no longer a predictor. It has been proposed that these early kinetics minimize the value of the *IFNL3* genotype, but the lead-in response is known only for patients who have initiated therapy. For the patient who is considering whether or not to undergo HCV therapy with the boceprevir regimen, *IFNL3* genotype remains the most helpful predictor of likelihood of response.[27]

Duration of therapy. Duration of treatment is another important factor for clinicians and patients to consider before initiating PEG-IFN-α and RBV therapy because patients with favorable *IFNL3* genotypes are more likely to respond to shorter

Table 2 Recommendations for use of PEG-IFN-α–containing regimens based on *IFNL3* genotype

Phenotype	Implications for PEG-IFN-α and RBV therapy[a]	Implications for protease inhibitor combinations with PEG-IFN-α and RBV therapy	Classification of recommendation[b]
Favorable response genotype	Approximately 70% chance for SVR[c] after 48 weeks of treatment. Consider implications before initiating PEG-IFN-α- and RBV-containing regimens.	Approximately 90% chance for SVR[c] after 24–48 weeks of treatment. Approximately 80–90% of patients are eligible for shortened therapy (24–28 weeks vs. 48 weeks).[d] Weighs in favor of using PEG-IFN-α- and RBV- containing regimens.	Strong
Unfavorable response genotype	Approximately 30% chance of SVR[c] after 48 weeks of treatment. Consider implications before initiating PEG-IFN-α- and RBV-containing regimens.	Approximately 60% chance of SVR[c] after 24–48 weeks of treatment. Approximately 50% of patients are eligible for shortened therapy regimens (24–28 weeks).[d] Consider implications before initiating PEG-IFN-α- and RBV-containing regimens.	Strong

HCV, hepatitis C virus; PEG-IFN-α, pegylated interferon-α 2a or 2b; RBV, ribavirin.

[a]In cases in which a protease inhibitor is not available. [b]See **Supplementary Tables S1–S4** online for additional details regarding the three-tiered system used to grade the quality of evidence and strength of recommendations by the Clinical Pharmacogenetics Implementation Consortium. [c]SVR, sustained virologic response (defined by undetectable serum viral RNA 12–24 weeks after the end of treatment). [d]Patients receiving boceprevir are eligible for treatment regimens of 24–28 weeks instead of the standard 48 weeks if HCV RNA is undetectable by week 8. Patients receiving telaprevir are eligible for 24 weeks of therapy instead of the standard 48 weeks if HCV RNA is undetectable by week 4.

treatment courses. Patients receiving boceprevir are eligible for 24- to 28-week regimens instead of the standard 48-week regimen if HCV RNA is undetectable by week 8.[27] In the boceprevir phase III clinical trial for treatment-naive patients, rs12979860 CC patients were more likely to have undetectable HCV RNA at week 8 (89%) than CT (53%) or TT (42%) patients.[26] SVR rates ranged from 81 to 100% for all patients in whom HCV RNA was undetectable by week 8, regardless of *IFNL3* genotype. With telaprevir therapy, patients with undetectable HCV RNA by week 4 are eligible for a treatment regimen of only 24 weeks.[27] Given the side-effect burden of PEG-IFN-α and RBV, the possibility of shorter treatment course may influence treatment choice for some patients.

Past treatment. In general, patients who have failed previous IFN-α-based therapies are enriched for the unfavorable *IFNL3* genotype; therefore, *IFNL3* genotype is less likely to influence clinical decisions. Analysis of phase III boceprevir trial results for patients who were treatment experienced found that *IFNL3* genotype did not predict SVR.[26] In patients with unclear records of their previous treatment or with questions about the quality of care received in a previous course of therapy, the *IFNL3* genotype can be considered a marker of IFN responsiveness that contributes to HCV treatment response.

IFNL3 single-nucleotide polymorphism concordance. Given that both rs12979860 and rs8099917 tests are available, clinicians may receive both pieces of data. The boceprevir phase III program conducted an analysis and found that combining rs12979860 and rs8099917 test results did not improve the strength of the association between the *IFNL3* genotype and SVR as compared with the results using rs12979860 genotype alone.[26] This analysis also found instances of discordance between rs12979860 and rs8099917. Most rs12979860 CC patients had the favorable TT pattern at the rs8099917 locus. However, of the 426 patients with the favorable TT genotype at the rs8099917 locus, only 208 (48.8%) also had the favorable CC genotype at the rs12979860 locus. This analysis of the boceprevir program reported that both rs12979860 and rs8099917 predict SVR, but rs12979860 is more reliable in this group of patients.

Other considerations

The original discovery of *IFNL3* genotype came from the analysis of treatment-naive patients with HCV genotype 1 treated with PEG-IFN-α and RBV, and subsequent studies have evaluated *IFNL3* genotype in other HCV patient groups.

Acute infection. With initial exposure to HCV, some patients are able to spontaneously clear the infection. Moreover, multiple well characterized cohort studies demonstrated that patients with the favorable *IFNL3* CC genotype are more likely to spontaneously clear the acute infection.[7,28–31] In the original analysis, the effect of rs12979860 variation was evaluated in six well-characterized cohorts of patients with acute HCV infection.[28] Patients with the favorable *IFNL3* CC genotype were more likely to clear infection spontaneously than patients with the CT/TT genotypes (53 vs. 28%), and results were similar in patients of European and African ancestry. Thus, *IFNL3* genotype testing may be informative for the treatment considerations for the acutely infected patient.

HCV genotypes 2 and 3. Outcomes for the treatment of chronic HCV genotypes 2 and 3 have consistently been better than those for HCV genotypes 1 and 4 with IFN-α-based regimens. SVR rates are higher for HCV genotypes 2 and 3 and can be achieved with a shorter therapy duration of 24 weeks.[3,32] Studies of patients with HCV genotypes 2 and 3 have not found that the *IFNL3* genotype is a predictor of response. The report by Mangia *et al.* did find that among patients in whom HCV RNA was not undetectable by week 4, SVR was achieved more often in rs12979860 CC patients as compared with CT and TT patients (87 vs. 67 and 29%, respectively; $P = 0.0002$).[33]

HIV/HCV coinfection. For patients with HIV/HCV coinfection, *IFNL3* genotype has been associated with spontaneous clearance and improved response to treatment with IFN-α-based regimens.[7,33] Rallon *et al.* evaluated a cohort of 164 treated HIV/HCV–coinfected patients, and 74% of patients with rs12979860 CC genotype achieved SVR as compared with 38% of patients with CT or TT genotypes ($P \leq 0.0001$).

Incidental findings

The *IFNL3* rs12979860 polymorphism has also been linked to HCV-induced hepatocellular carcinoma and graft fibrosis,[34] allergic disease in children,[35] liver fibrosis,[36] viral cirrhosis due to HCV,[37] and greater likelihood of HCV persistence, particularly in HCV genotypes 1 and 4.[38] The favorable rs12979860 CC genotype is associated with lower frequency of hepatic steatosis in patients with chronic HCV.[39] Carriers of the T allele of this variant have also been found to have increased susceptibility to chronic hepatitis B virus (HBV) infection and hepatocellular carcinoma as compared with noncarriers.[40]

POTENTIAL BENEFITS AND RISKS FOR THE PATIENT

Patients considering HCV therapy are confronted with medications with significant side effects and varying response rates. As a result, patients and clinicians must weigh the risks and benefits of treatment. Previous models of baseline characteristics had limited ability to accurately predict outcomes, and the best models incorporated early viral kinetics that required the patient to initiate treatment. At present, *IFNL3* genotype is the strongest baseline predictor of treatment response in patients receiving HCV therapy with PEG-IFN-α and RBV. With protease inhibitor regimens, *IFNL3* genotype predicts response and also predicts eligibility for the shorter durations of therapy. No clear risks have been determined with *IFNL3* genotype testing. Although not studied formally, knowledge of a reduced likelihood of response may result in fewer patients receiving HCV therapy that might have been effective.

CAVEATS: APPROPRIATE USE AND/OR POTENTIAL MISUSE OF GENETIC TESTS

IFNL3 genotype is a strong predictor of treatment response for patients receiving treatment for chronic HCV infection. However, genotyping alone does not provide the basis for the decision to treat or not to treat HCV infection. Patients with all *IFNL3* genotypes can respond to HCV therapy, and the differences in outcome are reduced with the addition of protease inhibitors. *IFNL3* genotype is one of several factors to be considered when estimating the likelihood of treatment response. In addition, the side-effect profile of HCV regimens should be considered independently from the likelihood of response according to *IFNL3* genotype.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/cpt

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The Clinical Pharmacogenetics Implementation Consortium guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision making and to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variations among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the health-care provider to determine the best course of treatment for a patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be made solely by the clinician and the patient. The Clinical Pharmacogenetics Implementation Consortium assumes no responsibility for any injury to persons or damage to persons or property arising out of or related to any use of the guidelines of the Clinical Pharmacogenetics Implementation Consortium or for any errors or omissions.

CONFLICT OF INTEREST

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