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Simeprevir Therapy and *IFNL3* Genotype

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Introduction

Simeprevir is a hepatitis C virus (HCV) protease inhibitor used in combination with other drugs to treat chronic hepatitis genotype 1 or 4 infection (1).

Previously, the standard care of patients with HCV infection was peginterferon alfa and ribavirin, but ~40-50% of patients with HCV genotype 1 infection had a suboptimal sustained virological response (SVR) (2).

A SVR is defined as undetectable HCV RNA by the end of treatment and at a specific number of weeks after the end of treatment. The addition of simeprevir increased the SVR in patients with HCV genotype 1 infection who were previously untreated. However, there were reports of treatment failure, most commonly in adults, who failed to respond to previous peginterferon and ribavirin treatment (3).

The FDA-approved drug label for simeprevir contains information regarding a genetic variant near the *IFNL3* gene (a C to T change; rs12979860), which is a strong predictor of response to peginterferon alfa and ribavirin treatment. The label states that in phase 3 clinical trials, SVR rates were lower in patients with CT and TT genotypes, compared to patients with the CC genotype. However, patients of all *IFNL3* genotypes had highest SVR rates when being treated with regimens that included simeprevir.

In addition, the label strongly recommends patients with HCV genotype 1a infection should be screened for the presence of virus with the S3 Q80K polymorphism. If Q80K is detected, the label strongly recommends that alternative therapy be considered (4).

Drug class: HCV Protease Inhibitors

The treatment of hepatitis C virus (HCV) has evolved over the years. Initially, interferon (IFN) was used as monotherapy. This was followed by the addition of the antiviral agent ribavirin (a nucleoside analogue) to peginterferon (PEG-IFN), and more recently, the addition of antiviral protease inhibitors such as simeprevir.

Protease inhibitors are the first direct-acting antivirals to be approved for the treatment of HCV, and simeprevir is the first second-generation agent to become available. Simeprevir has largely replaced the use of the first-generation protease inhibitors, boceprevir and telaprevir, which have less favorable side effect profiles.

Successful treatment of hepatitis C is confirmed when no trace of HCV can be found after treatment has finished. This is referred to as the SVR, which is defined as undetectable HCV RNA by a quantification assay at the end of treatment, and typically 12 (SVR12) or 24 weeks (SVR24) after the end of treatment.

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The addition of simeprevir to a PEG-IFN and ribavirin treatment regimen increases the SVR in patients with chronic hepatitis caused by genotype type 1 or 4 hepatitis C virus, and the response to treatment is influenced by the patient's *IFNL3* genotype.

The FDA-approved drug label for simeprevir states that simeprevir should only be used in combination with other antiviral drugs, such as in combination with PEG-IFN and ribavirin; or in combination with sofosbuvir (HCV nucleotide-analogue NS5B polymerase inhibitor) (1). However, because IFN-free regimes are fast becoming the current standard of care for hepatitis C, simeprevir tends to be prescribed with sofosbuvir rather than IFNs.

Drug: Simeprevir

Acute infection with HCV is usually asymptomatic, and about 15-45% of people who are infected clear the virus within 6 months of infection without any treatment. The remaining 55-85% of people will develop chronic HCV infection, which may also be asymptomatic for many years. It is thought that over 180 million people are infected with HCV worldwide (5).

The HCV is classified by genotype, based on the RNA viral strands. There are 6 classes of genotype, numbered 1-6, with multiple subtypes e.g., 1a, 1b, 2a, 2b. In the US, approximately 70% of people with HCV infection have genotype 1, with genotype 1a more common than 1b (6). Genotype 1 is the most difficult to treat, as it is less likely than genotypes 2 and 3 to respond to therapy.

Simeprevir has been FDA-approved for use in combination with other drugs, for the treatment of adults with chronic hepatitis C, caused by an infection with genotype 1 or 4 HCV.

During the natural course of HCV infection, patients develop liver fibrosis, which, without treatment, can progress to liver cancer (hepatocellular carcinoma). Approximately 45% of patients with chronic hepatitis C will develop liver cancer within 20 years from the initial infection.

Until recently, the standard of care for hepatitis C infection was based on therapy with peginterferon and ribavirin. Approximately half of the patients cleared the HCV infection, as shown by a SVR, but adverse effects were common and sometimes life-threatening (2). Treatment was expensive and inconvenient, lasting up to 48 weeks.

Protease inhibitors such as simeprevir were specifically developed to improve the effectiveness of peginterferon and ribavirin therapy. Teleprevir was the first drug to be developed, but severe dermatological adverse effects and liver toxicity limited its use. Simeprevir belongs to the second generation of drugs, and has an improved therapeutic index.

Simeprevir prevents maturation of the HCV by blocking viral protein synthesis. Specifically, simeprevir inhibits the viral protease NS3/4A which is responsible for cleaving and processing the HCV polyprotein precursor (7). Several mutations in this viral NS3/4A protease are associated with a reduced susceptibility to simeprevir. One of the most common and clinically significant mutations is the Q80K polymorphism. The FDA-approved drug label states that patients with HCV genotype 1a infection should be screened for the presence of virus with the Q80K polymorphism. If Q80K is detected, the label strongly recommends that alternative therapy be considered (1).

The combination of protease inhibitors such as simeprevir with peginterferon and ribavirin therapy has led to a much more effective treatment of hepatitis C in patients who were "treatment naïve" (no history of HCV treatment) and among "relapsers" (patients who had relapsed after previous HCV therapy). This was evidenced by improvement in the SVR and reduction of treatment from 48 to 24 weeks, without any increase in peginterferon and ribavirin adverse effects (3, 8).

The treatment options for hepatitis C continue to evolve. Currently, IFN-free treatment regimes for hepatitis C are considered to be the standard of care. The IFN-free combination of simeprevir plus sofosbuvir has been found to be a highly effective treatment, with studies reporting high SVR12 rates for the majority of patients with chronic HCV infection (from about 84% to 94%) (9-11).

Genetic variants in the *IFNL3* gene have been shown to strongly influence treatment response to PEG interferon-alpha-based regimens (including regimens with simeprevir) in previously untreated patients with HCV genotype 1 infection (4). However, data are currently lacking on how *IFNL3* variants influence an individual's response to simeprevir when used with sofosbuvir in an IFN-free regimen.

Gene: *IFNL3*

The *IFNL3* gene, previously known as *IL28B*, encodes interferon lambda-3 (IFN-λ3) and is involved in the immune response to hepatitis C.

When a person is infected by a virus, their immune response includes the production of interferons. These signaling proteins induce changes in infected and uninfected cells to block viral replication and stop the spread of virus. Interferons are given as part of treatment for HCV to strengthen this innate response.

There are three classes of IFNs: type I (IFN-α/β), type II (IFN-γ) and type III (IFN-λ). The IFNL3 is a type III interferon, and as such, induces a strong antiviral state in responsive cells with a higher risk of viral infection, such as mucosal cells (12).

IFNL3 is only highly expressed in hepatocytes and epithelial cells, in contrast to other similar interferons, such as IFN-α, which are expressed in most cell types. IFNL3 exerts its actions by interacting with a cytokine receptor complex, which is composed of the IL10RB and IL28RA receptor chains (4).

The first two *IFNL3* variants to be commonly tested for are rs12979860 and rs8099917. These variants are in close proximity to each other near the *IFNL3* gene, and are in strong linkage disequilibrium. HCV genotype 1 patients with the "favorable" genotypes (CC for rs12979860 and TT for rs8099917) respond better to treatment as they are associated with an approximate 2-fold increase in SVR. However, the exact mechanism how these variants influence treatment outcome is not yet known (4).

In a US cohort of mixed ethnicity, variants in rs12979860 predicted treatment response in HCV genotype 1 infection patients: CC genotype individuals were more likely to spontaneously clear acute HCV infection and TT genotype individuals had the poorest response to treatment. Accordingly, CT genotype individuals had an intermediate response that was between those of the CC and TT genotype patients (4).

The response to HCV treatment varies across different populations, which can be largely explained by differences in allele frequencies. The rs12979860 'C' allele is commonly found in East Asians (allele frequency nearly 0.9), followed by Caucasians (0.63) and Hispanics (0.55), and is the least common among individuals of African origin (0.39) (4).

Among Asians and individuals of European descent, the rs8099917 variant best predicts treatment response (13-15). Moreover, recently a variant in the *IFNL4* gene (rs368234815), was found to be superior to rs12979860 in predicting treatment outcome in individuals of African ancestry. Together with another *IFNL4* variant (rs117648444), the combination of these two variants was found to have greater treatment response prediction compared to testing for single variants (12).

Genetic Testing

Genetic testing for *IFNL3* is available, and is used to predict response to peg-IFN and RBV in HCV genotype 1 patients. The results can help clinicians and patients make informed decisions on how to best manage their HCV infection.

The rs12979860 variant is most commonly tested, and the results are typically reported in the following format:

rs12979860 CC, favorable genotype

rs12979860 CT, unfavorable genotype

rs12979860 TT, unfavorable genotype (4).

Before starting a treatment regimen with simeprevir in patients with HCV genotype 1a infection, the FDA strongly recommends screening patients for the presence of virus with the "NS3 Q80K" polymorphism. The FDA states that an alternative therapy to simeprevir should be considered if Q80K is detected (1).

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2015 Statement from the US Food and Drug Administration (FDA): A genetic variant near the gene encoding interferon-lambda-3 (IL28B rs12979860, a C [cytosine] to T [thymine] substitution) is a strong predictor of response to Peg-IFN-alfa and RBV (PR). In the Phase 3 trials, IL28B genotype was a stratification factor.

Overall, SVR rates were lower in subjects with the CT and TT genotypes compared to those with the CC genotype. Among both treatment-naïve subjects and those who experienced previous treatment failures, subjects of all IL28B genotypes had the highest SVR rates with simeprevir-containing regimens.
Please review the complete therapeutic recommendations that are located here: (1)

Nomenclature

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
rs12979860	/	NM_001276254.2:c.151-152G>A	N/A	rs12979860
rs8099917	/	N/A	N/A	rs8099917

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS): http://www.hgvs.org/content/guidelines

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[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug.

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