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Sofosbuvir Therapy and *IFNL4* Genotype

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Introduction

Sofosbuvir is an antiviral agent used in the treatment of chronic hepatitis C virus (HCV) infection. Sofosbuvir is FDA-approved to treat patients infected with HCV genotypes 1, 2, 3, and 4, as part of a combination antiviral treatment regimen (1). HCV genotype 1 is the most prevalent worldwide and HCV genotype 3 is the next most prevalent (2). Sofosbuvir may also be used as part of the treatment regimen of HCV genotypes 5 or 6 (3).

About 180 million people worldwide are infected with chronic hepatitis C, which is a major cause of chronic liver disease, cirrhosis, and liver cancer. Viral eradication is suboptimal with peginterferon plus ribavirin-based therapy, with only about half of patients with HCV genotype 1 infection achieving a sustained virological response (SVR) after 24 weeks (4). A SVR is defined as undetectable HCV RNA by the end of treatment or at a specific number of weeks after the initiation of treatment, e.g., undetectable HCV RNA at 12 weeks is annotated (SVR12).

Direct-acting antivirals (DAAs), such as sofosbuvir, were developed to improve viral eradication rates. They target HCV-encoded proteins involved in viral replication and infection. Sofosbuvir, the first and thus far only DAA, targets NS5B polymerase, the viral enzyme required for HCV RNA replication.

Sofosbuvir may be used in combination with peginterferon. The genetic variant rs12979860, located in the *INFL4* gene, is a strong predictor of response to peginterferon-based therapies. The variant is a C to T change—individuals with the favorable "C/C" genotype have about a 2-fold higher likelihood of achieving SVR compared to individuals with CT or TT genotypes (5). (Note, because the association of rs12979860 with treatment response was reported several years before the discovery of *IFNL4*, the variant is commonly, but mistakenly, referred to as *IL28B*, which is the previous name for the *IFNL3* gene.)

For specific treatment regimens that include sofosbuvir, although the *IFNL4* variant still influences treatment outcomes, the SVR remains relatively high for all *IFNL4* genotypes. For example in the NEUTRINO study, which is referred to in the FDA-approved drug label for sofosbuvir, the SVR12 rate was 99% in individuals with baseline C/C alleles and 87% in individuals with baseline non-C/C alleles. The individuals in this study had HCV genotype 1 or 4 infection, and were receiving sofosbuvir plus peginterferon plus ribavirin therapy (1, 6).

The drug label for sofosbuvir also discusses viral resistance. In cell culture, the amino acid substitution S282T in the viral NS5B polymerase is associated with reduced susceptibility to sofosbuvir (7). During the ELECTRON trial, this substitution was transiently detected in one individual who relapsed during sofosbuvir monotherapy. However, the clinical significance of such substitutions remains unknown (1).

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Drug Class: Direct Acting Antivirals for HCV

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. However, only about half of the HCV genotype 1-infected patients cleared their infection, and adverse effects were common and sometimes life-threatening (4). Treatment was also expensive and inconvenient, lasting up to 48 weeks.

Direct-acting antivirals (DDAs) improved the effectiveness of peginterferon and ribavirin therapy. These agents target specific viral proteins required for viral replication and infection.

HCV is a single-stranded RNA virus that encodes structural proteins (to encode the viral capsid and envelope) and non-structural proteins (required for viral replication). The DDAs target several of the non-structural proteins, the viral protease (NS3/NS4A), the viral RNA polymerase (NS5B), and a viral protein thought to regulate replication and viral assembly (NS5A).

Currently, there are four classes of drugs in clinical use or in development, which are classified by their therapeutic target:

- Protease inhibitors e.g., simeprevir, grazoprevir, paritaprevir
- Nucleoside polymerase inhibitors e.g., sofosbuvir
- Non-nucleoside polymerase inhibitors
- NS5A inhibitors e.g., ledipasvir

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.

Drug: Sofosbuvir

Sofosbuvir is a nucleotide analogue used in the treatment of chronic HCV infection as part of a combination antiviral treatment regimen.

The early stages of infection with HCV are usually asymptomatic—about 15-45% of people spontaneously 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 (8).

However, during the natural course of HCV infection, patients develop liver fibrosis, which, without treatment, can progress to liver cirrhosis and liver cancer (hepatocellular carcinoma). The risk of developing liver cancer for a patient with HCV-related cirrhosis is approximately 2-6% per year (9).

HCV is classified by genotype, based on the nucleotide sequence of the viral RNA. There are six major 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 (8). Genotype 1 was formerly the most difficult to cure with interferon-based therapies, as it was less likely than genotypes 2 and 3 to respond to therapy. With the introduction of DAA-based, interferon-free treatments, this is no longer the case.

Sofosbuvir is indicated for the treatment of genotype 1, 2, 3 or 4 chronic HCV infection and is generally considered to have moderate to high efficacy for all six genotypes (10). For the treatment of genotype 1 or 4 infections, the drug label recommends a combination therapy of sofosbuvir plus peginterferon alfa plus ribavirin. For the treatment of genotype 2 or 3 infections, the combination therapy of sofosbuvir plus ribavirin is recommended (1).

Sofosbuvir is a NS5B nucleotide analogue and a prodrug. Once inside a liver cell, sofosbuvir is activated by phosphorylation to a nucleoside triphosphate that competes with nucleotides during viral replication. Binding of the analogue to the viral NS5B polymerase results in RNA chain termination, thus inhibiting the virus from replicating its genome (11).

The safety and efficacy of sofosbuvir has been established in several clinical trials. The usual dose of sofosbuvir is a 400mg tablet, taken once a day for 12 weeks, in combination with other antiviral agents. Sofosbuvir is generally well tolerated, with no side effects beyond those associated with placebo therapy (10, 12).

Sofosbuvir forms the backbone of a several treatment regimens including DAA such as sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir. The regimen sofosbuvir/ ledipasvir has been found to result in high SVR rates in shorter periods of time, but costs may be prohibitive (7).

Genetic variants in the *IFNL4* gene have been shown to strongly influence treatment response to peginterferon-based regimens in previously untreated patients with HCV genotype 1 infection (5, 13). Such variants also appear to influence the outcomes of treatment regimens that include sofosbuvir. For example, the rs12979860 genotype predicts the response to 8 weeks of treatment with sofosbuvir/ledipasvir (14).

In addition, several substitutions that occur with the viral NS5B polymerase have been reported. Most notably, a S282T polymorphism has been associated with sofosbuvir resistance (15). In cell cultures, the S282T substitution is associated with a reduced susceptibility to sofosbuvir. However, the clinical significance of such substitutions is not yet known, as they appear to be detrimental to viral fitness. So far, the S282T substitution has only been detected in one patient who experienced a relapse while being treated with sofosbuvir monotherapy in a trial, and the substitution was no longer detectable at week 12 post-treatment (1).

Gene: *IFNL4*

The *IFNL4* gene encodes interferon lambda-4 (IFN-λ4) and is involved in the immune response to hepatitis C.

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

Three classes of IFNs exist: type I (IFN-α/β), type II (IFN-γ), and type III (IFN-λ). The most recent interferon to be discovered, *IFNL4*, belongs to the type III class. It is located upstream of *IFNL3* and is a functional gene in the majority (>95%) of the African population. But in about 50% of the European population and in most of the east Asian population, IFNL4 is a pseudogene, created by a frameshift-causing deletion polymorphism (rs368234815) (16-18).

As a type III interferon, IFNL4, induces an antiviral state in responsive cells with a higher risk of viral infection, such as mucosal cells (17). IFNL4 exerts its actions by interacting with a cytokine receptor complex, which is composed of the IL10RB and IFNLR1 receptor chains (5). Expression of IFNLR1 is largely restricted to cells of epithelial origin, which includes hepatocytes. In contrast, receptors for type I interferons, such as IFN-α, are expressed in most cell types.

The first two variants to be commonly tested for are rs12979860 (located in *IFNL4*) and rs8099917, which lies proximate to *IFNL4*. These variants are in close proximity to each other and are in strong linkage disequilibrium (5). Linkage disequilibrium means that the variants are linked to treatment response more than would be expected in the general population.

HCV genotype 1 patients with the "favorable" genotypes (CC for rs12979860 and TT for rs8099917) respond better to interferon-based treatment—favorable genotypes are associated with an approximate 2-fold increase in

SVR (5). However, for specific treatment regimens which include sofosbuvir, although an individual's *IFNL4* genotype still influences treatment outcomes, the SVR for non-favorable genotypes remains relatively high (1).

In the NETURINO study, patients with HCV genotype 1 or 4 who had not received previous treatments for HCV infection were treated with a regimen of sofosbuvir plus peginterferon plus ribavirin for 12 weeks. The SVR12 rate was 99% (89/90) in subjects with baseline rs12979860 C/C alleles and 87% (200/230) in subjects with baseline rs12979860 non-C/C alleles (6).

Similarly, in the PHOTON trial, patients with HCV genotype 1 infection and co-infection with HIV were treated with a combination of sofosbuvir and ribavarin. The SVR12 rates were 80% (24/30) in subjects with baseline rs12979860 C/C allele and 75% (62/83) in subjects with baseline rs12979860 non-C/C alleles (1).

The frequency of the rs12979860 'C' allele varies globally across different populations—it 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) (5).

In individuals of African ancestry, the rs368234815 variant is superior to rs12979860, and together with another *IFNL4* variant (rs117648444), the combination of testing these two variants gives a greater treatment response prediction compared to testing for single variants (16, 17).

Genetic Testing

Genetic testing for *IFNL4* is used to predict response to peginterferon and ribavarin in HCV genotype 1 patients. The results can help clinicians and patients make informed decisions on how to manage 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 (5).

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.

Statement from the US Food and Drug Administration (FDA): NEUTRINO was an open-label, single-arm trial that evaluated 12 weeks of treatment with sofosbuvir in combination with peginterferon alfa 2a and ribavirin in treatment-naïve subjects with genotype 1, 4, 5 or 6 HCV infection compared to pre-specified historical control. [...] SVR12 rates were 99% (89/90) in subjects with genotype 1 or 4 HCV and baseline IL28B C/C allele and 87% (200/230) in subjects with genotype 1 or 4 HCV and baseline IL28B non-C/C alleles[2].

It is estimated that the SVR12 in patients who previously failed pegylated interferon and ribavirin therapy will approximate the observed SVR12 in NEUTRINO subjects with multiple baseline factors traditionally associated with a lower response to interferon-based treatment. The SVR12 rate in the NEUTRINO trial in genotype 1

[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.

[2] Note: Recent studies report that the rs12979860 variant is in the IFNL4 gene, and not the IFNL3 gene (previously called IL28B). Therefore, a more accurate term for describing an individual's genotype would be "rs12979860 C/C", instead of "IL28B C/C".

subjects with IL28B non-C/C alleles, HCV RNA greater than 800,000 IU/mL and Metavir F3/F4 fibrosis was 71% (37/52).

[…]

In a pooled analysis of 982 subjects who received sofosbuvir in Phase 3 trials, 224 subjects had post- baseline NS5B genotypic data from next generation nucleotide sequencing (assay cutoff of 1%).

Treatment-emergent substitutions L159F (n=6) and V321A (n=5) were detected in post-baseline samples from GT3a-infected subjects across the Phase 3 trials. No detectable shift in the phenotypic susceptibility to sofosbuvir of subject isolates with L159F or V321A substitutions was seen. The sofosbuvir-associated resistance substitution S282T was not detected at baseline or in the failure isolates from Phase 3 trials. However, an S282T substitution was detected in one genotype 2b subject who relapsed at Week 4 post-treatment after 12 weeks of sofosbuvir monotherapy in the Phase 2 trial P7977-0523 [ELECTRON]. The isolate from this subject displayed a mean 13.5-fold reduced susceptibility to sofosbuvir. For this subject, the S282T substitution was no longer detectable at Week 12 post-treatment by next generation sequencing with an assay cutoff of 1%.

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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