Predictors of response to antiviral therapy for chronic hepatitis C virus infection

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INTRODUCTION

The introduction of direct-acting antiviral (DAA)-based therapies for chronic hepatitis C virus (HCV) infection has revolutionized the approach to HCV treatment, resulting in highly efficacious and well-tolerated therapy for nearly all patients. Because of such high success rates (over 90 percent for most populations), patient and viral features that historically predicted worse outcomes with interferon-based regimens have a limited impact on responses to combination DAA regimens. Rather than identify patients with a much lower chance of attaining cure (who thus might have forgone interferon-based therapy), such features influence treatment strategies with DAA regimens, such as duration of treatment and the need for the addition of ribavirin.

This topic reviews the patient and viral features that impact response to and selection of interferon-free combination DAA regimens for chronic HCV infection. The diagnosis of chronic HCV infection and the evaluation of patients prior to HCV treatment are discussed in detail separately. (See "Screening and diagnosis of chronic hepatitis C virus infection" and "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection".)

Specific regimen selection is discussed separately. (See "Management of chronic hepatitis C virus infection: Initial antiviral therapy in adults" and "Management of chronic hepatitis C virus infection: Antiviral retreatment following relapse in adults".)

HISTORICAL PERSPECTIVE

Traditional predictors of response to interferon-based HCV therapy included both patient and viral factors. Patient factors that were associated with worse response to interferon-based therapy included male sex, older age, high body mass index (BMI), advanced liver fibrosis, history of failed treatment, being of a Black population, non-CC IL28B genotype, and the presence of certain comorbid conditions, such as HIV coinfection, insulin resistance, or diabetes. Viral factors that were associated with worse response included non-genotype-2 infection, high viral load, and unfavorable viral kinetics during treatment (eg, slow decline or rebound in viral level).

With interferon-based therapies, these factors played a prominent role in management decisions, in three ways:

- To estimate the likelihood of response to a given course of therapy and frame the discussion of whether treatment should be initiated or deferred for a given patient. Prominent predictors in this category included:
  - HCV genotype
  - History of prior HCV treatment
  - Cirrhosis status
  - HIV coinfection
  - Baseline HCV RNA level
- To select the specific treatment regimen (eg, duration of interferon plus ribavirin and dosing of ribavirin). HCV genotype (typically genotype 1 versus 2 or 3) was the main factor to inform this decision.
- To determine whether to discontinue treatment mid-course because of futility. On treatment viral response (ie, HCV RNA levels at weeks 12 and 24 of therapy) was the main factor to inform this decision.

With interferon-free direct-acting antiviral (DAA) regimens, several of these traditional predictors of response are no longer relevant, and for those that remain relevant, the main role is to inform regimen selection and duration.

FACTORS THAT IMPACT REGIMEN SELECTION

Despite universally high response rates to direct-acting antiviral (DAA) regimens, a number of "traditional" factors must still be considered prior to starting therapy for chronic HCV infection. The two most important factors are:

- Presence of cirrhosis (see 'Cirrhosis status' below)
- HCV treatment history (see 'Prior treatment failure' below)

A third factor, viral genotype and subtype (see 'HCV genotype and subtype' below), also played a critical role early in the interferon-free DAA era. However, as pangenotypic DAA regimens have become available, the importance of genotype and subtype has waned, particularly for treatment-naïve patients without cirrhosis, who comprise the majority of patients undergoing antiviral therapy. With use of pangenotypic regimens, pretreatment genotyping is generally not required for regimen selection, although some payors may still require the information before authorizing the medication.

Since DAA agents bind to and target the virus itself, pre-existing viral polymorphisms that confer resistance to these agents (termed resistance-associated substitutions [RASs]) have emerged as a new predictor of response to treatment. The impact of RASs is highly dependent on other patient and viral factors, as well as the specific DAA regimen being considered. (See 'Resistance-associated substitutions' below.)

Cirrhosis status — Determining the stage of liver fibrosis for a given patient is a critical component of HCV management, both to select the appropriate antiviral regimen and to ensure that appropriate medical evaluations and cancer screenings are undertaken. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'Assessment of fibrosis stage' and "Cirrhosis in adults: Overview of complications, general management, and prognosis".)

For most genotypes, the sole presence of compensated cirrhosis is no longer a major predictor of a poor response to therapy, as regimen modifications for patients with cirrhosis can yield sustained virologic response (SVR) rates that are similar to those observed in patients without cirrhosis. The exception is patients with chronic genotype 3 infection, in whom cirrhosis is the predominant feature associated with poorer response, which may not be completely overcome by the extension of therapy or the addition of ribavirin [1-3]. (See 'Role in genotype 3' below.)

The mechanism behind impaired treatment response in patients with cirrhosis is uncertain but may involve altered drug delivery/metabolism and an increased risk of drug toxicity [4].

Role in genotype 1 — For some genotype 1 regimens (including pangenotypic regimens), cirrhosis has no substantial impact and does not warrant regimen modification. For certain

other regimens, adjustments such as increasing the duration and/or adding ribavirin may be needed so that patients with cirrhosis can achieve response rates similar to those without cirrhosis. (See "Management of chronic hepatitis C virus infection: Antiviral retreatment following relapse in adults", section on 'Relapse after glecaprevir-pibrentasvir'.)

As an example, in an integrated analysis of patients with cirrhosis treated with ledipasvir-sofosbuvir with or without ribavirin for 12 to 24 weeks, the largest negative impact of cirrhosis on SVR was among treatment-experienced patients who received the regimen for 12 weeks without ribavirin (SVR rate 90 percent) [5]. This negative impact of cirrhosis was largely abrogated by the addition of ribavirin (SVR rate 96 percent) or the extension of therapy to 24 weeks (SVR rate 98 percent), which resulted in response rates comparable with those observed among patients without cirrhosis.

Cirrhosis does not appear to be a significant factor impacting treatment response with sofosbuvir-velpatasvir [6], glecaprevir-pibrentasvir [7], or elbasvir-grazoprevir in the absence of RASs [8]. In fact, for elbasvir-grazoprevir, most studies have shown a numerically slightly higher SVR rate in those with cirrhosis [9,10].

Role in genotype 2 — Responses to DAA-based therapy are very high in most patients with genotype 2 regardless of the presence of cirrhosis, particularly with sofosbuvir-velpatasvir and glecaprevir-pibrentasvir [6,11,12].

Role in genotype 3 — Cirrhosis status remains one of the most important predictors of response for most regimens in patients with genotype 3 infection.

- **Regimens with** sofosbuvir **plus a NS5A inhibitors** – For regimens that combine sofosbuvir with a NS5A inhibitor (ie, velpatasvir or daclatasvir), outcomes are not quite as good in the presence of cirrhosis.

  In a study of sofosbuvir-velpatasvir for 12 weeks, SVR rates were 91 percent in patients with cirrhosis compared with 97 percent in those without [2]. In a subsequent randomized, open-label trial, adding ribavirin to the regimen was associated with a higher SVR rate (96 versus 91 percent) and a corresponding reduction in virologic failure (2 versus 6 percent) in patients with genotype 3 infection and cirrhosis [13]. The favorable impact of ribavirin was most pronounced among patients who had baseline NS5A RASs (SVR in 96 versus 84 percent without ribavirin). Although the study was underpowered and these differences were not statistically significant, these results support recommended treatment approaches. (See "Management of chronic hepatitis C virus infection: Initial antiviral therapy in adults", section on 'Known genotype 3 infection'.)

The differences in SVR between patients with and without cirrhosis appear even greater with daclatasvir plus sofosbuvir (63 versus 96 percent), although these outcomes are based on relatively few patients with cirrhosis [1]. Limited data also suggest that adding ribavirin to the daclatasvir plus sofosbuvir and extending the duration to 24 weeks are associated with improved outcomes, although it is uncertain if these modifications fully negate the impact of cirrhosis.

- Glecaprevir-pibrentasvir – For glecaprevir-pibrentasvir, data do not suggest an adverse impact of cirrhosis on response to either an 8- or 12-week course [7,14,15]. In one trial, 12 weeks of glecaprevir-pibrentasvir resulted in an SVR rate of 98 percent among 40 treatment-naïve genotype 3-infected patients with cirrhosis [14], similar to response rates in patients with other genotypes [12]. Response rates to this regimen seem more associated with history of treatment. (See 'Prior treatment failure' below.)

- Sofosbuvir-velpatasvir-voxilaprevir – Even for the most potent triple-combination regimens, such as sofosbuvir-velpatasvir-voxilaprevir, cirrhosis is associated with slightly lower response rates in genotype 3 infection. In patients with genotype 3 infection who had failed prior NS5A inhibitor-based DAA therapy, SVR rates with 12 weeks of sofosbuvir-velpatasvir-voxilaprevir were 100 percent in patients without cirrhosis, compared with 93 percent in those with cirrhosis [16]. Subsequent “real-world” studies of sofosbuvir-velpatasvir-voxilaprevir for treatment after DAA failure have continued to show that genotype 3 infection with cirrhosis is associated with lower SVR rates [17,18]. (See "Management of chronic hepatitis C virus infection: Antiviral retreatment following relapse in adults", section on 'Relapse after sofosbuvir-velpatasvir (or other sofosbuvir-NS5A combination)'.)

Decompensated cirrhosis — Patients with a history of decompensated cirrhosis (ascites, hepatic encephalopathy, or gastroesophageal variceal hemorrhage (table 1)) represent a unique subset of patients with a worse response to HCV therapy compared with those who have compensated cirrhosis. Treatment options are further limited for this population since NS3 protease inhibitors are relatively contraindicated in patients with decompensated cirrhosis.

In the limited number of HCV treatment studies in patients with decompensated HCV cirrhosis, SVR rates appear lower among those with Child-Pugh class C liver disease compared with those with Child-Pugh class A or B disease [19-21]:

- 56 versus 92 to 94 percent with sofosbuvir plus daclatasvir plus ribavirin for 12 weeks
- 72 to 85 versus 87 to 96 percent with ledipasvir-sofosbuvir plus ribavirin for 12 to 24 weeks

The majority of these studies have included ribavirin in the treatment regimen, which appears important for achieving maximal SVR rates in patients with decompensated cirrhosis. In a trial of sofosbuvir-velpatasvir patients with Child-Pugh class B disease, SVR rates were higher when ribavirin was included in the regimen (94 percent with ribavirin for 12 weeks versus 83 and 86 percent without ribavirin for 12 to 24 weeks) [22]. Unless absolutely contraindicated, ribavirin should be included, starting at 600 mg and increasing as tolerated. (See "Management of chronic hepatitis C virus infection: Initial antiviral therapy in adults", section on 'Decompensated cirrhosis (Child-Pugh class B or C)' and "Management of chronic hepatitis C virus infection: Antiviral retreatment following relapse in adults", section on 'Patients with decompensated cirrhosis'.)

Depending on individual circumstances, it is often prudent to pursue liver transplantation prior to attempting to treat HCV infection in those with advanced decompensated liver disease (Child-Pugh class C). (See "Liver transplantation in adults: Patient selection and pretransplantation evaluation".)

Prior treatment failure — The impact of prior interferon-based treatment itself is modest and infrequently impacts HCV treatment approaches with combination DAA regimens in the absence of other negative predictors. The key aspects in determining the impact of prior treatment are the type of prior HCV treatment (ie, peginterferon plus ribavirin, peginterferon plus ribavirin plus a DAA, or an interferon-free DAA-based regimen) and other patient characteristics, most notably the presence or absence of cirrhosis.

- **Failure of prior peginterferon and** ribavirin – For genotype 1 infection, prior treatment with peginterferon and ribavirin generally only impacts treatment approaches with certain regimens in the setting of cirrhosis. (See 'Role in genotype 1' above.)

  For genotype 3 infection, the apparent impact of prior treatment with peginterferon and ribavirin on outcomes with different DAA therapies is mixed. In the absence of cirrhosis, treatment-experienced patients had generally comparable SVR rates to treatment-naïve patients with sofosbuvir plus daclatasvir for 12 weeks (94 versus 97 percent) [1], whereas the difference was slightly larger between treatment-experienced and -naïve patients who received sofosbuvir-velpatasvir (90 versus 98 percent) [2]. With glecaprevir-pibrentasvir, prior treatment failure is associated with numerically lower response rates to a 12-week course (91 versus 95 percent among treatment-naïve patients), which can be improved with a 16-week duration (to 95 percent), although numbers in this trial are relatively small [14]. (See "Management of chronic hepatitis C virus infection: Antiviral retreatment following relapse in adults", section on 'Regimen selection for relapse after interferon-based regimens'.)

- **Failure of prior peginterferon plus** ribavirin **plus a protease inhibitor** – For genotype 1-infected patients, prior failure with peginterferon, ribavirin, and a protease inhibitor (typically telaprevir or boceprevir) does not appear to impact subsequent therapy with the combination of sofosbuvir with a NS5A inhibitor (ledipasvir, velpatasvir, daclatasvir) [6,23,24]. With earlier generation protease inhibitors (eg, simeprevir, paritaprevir), there was concern for cross-resistance in patients who had failed other early-generation protease inhibitors. However, both grazoprevir and glecaprevir have an improved resistance profile and may be less affected by prior protease inhibitor exposure. In a study of 79 patients who had failed peginterferon plus ribavirin plus a protease inhibitor (telaprevir, boceprevir, or simeprevir), elbasvir-grazoprevir plus ribavirin for 12 weeks resulted in SVR in 96 percent [25]. Similarly, in a study of 52 patients with prior protease inhibitor exposure (without NS5A inhibitor exposure), glecaprevir-pibrentasvir for 12 to 16 weeks with or without ribavirin resulted in SVR in 100 percent [26,27].

- **Failure of prior sofosbuvir-containing regimen** – Failure of prior sofosbuvir plus ribavirin (with or without peginterferon) does not appear to impact response to retreatment of patients with genotype 1 infection. This may be due in part to the fact that resistance to sofosbuvir is rarely seen in patients failing a sofosbuvir-containing regimen and the major sofosbuvir RAS S282T, if selected for, does not persist [28]. In a study of 50 genotype 1-infected patients who previously failed a sofosbuvir-containing regimen (that did not include an NS5A inhibitor), all achieved SVR with ledipasvir-sofosbuvir plus ribavirin for 12 weeks [29].

  Data on the impact of prior sofosbuvir failure on response to retreatment in patients with genotypes 2 or 3 infection are extremely limited. Importantly, the majority of these patients are likely to have genotype 3 infection and cirrhosis, two characteristics which are likely to outweigh any impact of prior sofosbuvir exposure. (See 'Role in genotype 3' above.)

  For most trials of glecaprevir-pibrentasvir in treatment-experienced patients, prior sofosbuvir exposure without another DAA was not exclusionary, so expected response rates with this regimen for such patients are generally the same as for interferon experienced [12,14].

- **Failure of other combination DAA regimens (including NS5A inhibitors)** – Given the rarity with which patients fail current DAA regimens, the impact of prior DAA treatment failure on retreatment approaches and responses has not been extensively studied. However, both the inclusion of NS5A inhibitors in most contemporary initial DAA treatment regimens and the existence of substantial cross-resistance within this class pose potential

issues for retreatment. This population is also likely to be enriched for other negative predictors of response making an assessment of the contribution of DAA treatment failure itself difficult. The most concerning result of DAA failure is the development of DAA-specific resistance which may limit retreatment options and responses. (See 'Resistance-associated substitutions' below.)

Data support the approach of using combination regimens composed of three drug classes (NS5B nucleotide, NS3 protease inhibitor, and NS5A inhibitor) to retreat HCV infection in patients who failed a prior interferon-free treatment regimen, particularly those that had an NS5A inhibitor as a component of their initial treatment. In a study of sofosbuvir-velpatasvir-voxilaprevir for 12 weeks, high SVR rates (96 percent) were seen across all genotypes [16].

HCV genotype and subtype — The viral genotype remains an important factor in DAA regimen selection, particularly in the setting of cirrhosis or prior treatment failure. Some DAA agents are genotype specific and have no or poor activity against other genotypes. Occasionally, treatment approaches with pangenotypic regimens (eg, duration and the need to add ribavirin) still vary by genotype. Specific regimen selection is discussed in detail separately. (See "Management of chronic hepatitis C virus infection: Initial antiviral therapy in adults" and "Management of chronic hepatitis C virus infection: Antiviral retreatment following relapse in adults".)

Genotype 1 virus is the most prevalent genotype worldwide, including in the United States (figure 1) [30,31]. Development of novel therapies for chronic HCV infection had initially focused on genotype 1 infection, and so there are many highly effective DAA regimen options for this genotype. Genotype 1 virus is divided into two major subtypes, 1a and 1b. Subtype 1a is the most common in the United States. Determination of viral subtype was necessary for proper regimen selection with certain early DAA regimens such as ombitasvir-paritaprevir-ritonavir plus dasabuvir and elbasvir-grazoprevir, as SVR rates were lower for subtype 1a than 1b when these regimens were given without ribavirin [32,33]. However, these regimens are either unavailable or infrequently used; the widespread use of pangenotypic regimens (eg, sofosbuvir-velpatasvir and glecaprevir-pibrentasvir) has reduced the need for appropriate subtype characterization, as SVR rates with these regimens are similarly high for both genotype 1 subtypes [6,7]. SVR rates with other, non-pangenotypic sofosbuvir-containing regimens are also similar between subtypes 1a and 1b (table 2).

Among non-genotype 1 infections, genotype 3 infection is the most significant predictor of a poor treatment response, particularly if the patient is treatment experienced or has cirrhosis (see 'Role in genotype 3' above). In studies of various DAA regimens, SVR rates with genotype 3 infection are at least numerically lower than with other genotypes [1,7,14,34,35].

Genotype 2 infections respond to the same treatment regimens as genotype 3, with higher SVR rates [7,9,11,34,35]. Genotype 2 infections are so responsive to DAA agents that it is unlikely that other baseline predictors will have any substantial impact on treatment responses. As an example, in a study that evaluated sofosbuvir-velpatasvir for 12 weeks in 238 genotype 2-infected patients, including a limited number of patients with cirrhosis and/or prior treatment failure, 237 (99.6 percent) achieved SVR, with one patient discontinuing the study regimen prematurely [2,6]. Similarly, high SVR rates for genotype 2 are seen with glecaprevir-pibrentasvir, given for 8 or 12 weeks, regardless of other patient or virus characteristics [11,15].

Data remain limited for genotypes 4, 5, and 6; however, these genotypes do not appear to be associated with a significantly lower response than genotype 1 infection and respond similarly to pangenotypic regimens [6,11].

Resistance-associated substitutions — Because of the error-prone nature of the HCV RNA polymerase, replication during chronic infection results in the generation of numerous genetic sequence polymorphisms, some of which also result in amino acid changes that can confer resistance to a given DAA, known as resistance-associated substitutions (RASs). In the absence of selective pressure from drug exposure, the majority of these polymorphisms are not replicatively fit enough to establish themselves as a significant component of the viral quasispecies (see "Characteristics of the hepatitis C virus", section on 'Quasispecies'). Nevertheless, in a subset of patients and clinical circumstances, RASs do impact response to therapy and may necessitate a change in treatment approaches to achieve optimal responses.

While a consensus on the methods for RAS assessment and reporting has not been firmly established, emerging data suggest that population sequencing (which can generally detect a RAS present in at least 15 to 20 percent of the viral population) identifies the vast majority clinically significant RASs [36,37]. Next generation sequencing (NGS) can identify RASs that are present in only 1 percent of the viral quasispecies, but reporting polymorphisms present at this threshold results in identification of clinically irrelevant RASs [36,38]. Instead, using a 10 to 15 percent cutoff for identification and reporting of RASs with NGS is expected to yield results similar to population sequencing, although head-to-head comparisons evaluating clinical outcomes are not available.

In the United States, two major commercial HCV RAS tests are available, one based on population sequencing and one based on NGS, which reports RASs that are present in at least 10 percent of the viral quasispecies. Both assays are available for the NS3 protease, NS5B polymerase, and NS5A genes in genotypes 1a, 1b, and 3 viruses. Given the apparent equipoise in identifying clinically significant RASs, either test may be used to guide patient management

when needed. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'Viral resistance testing'.)

Baseline RASs — Baseline RASs refer to polymorphisms that confer resistance to a particular DAA class and are present in the patient's virus despite no prior exposure to those agents. The prevalence of baseline RASs varies according to the viral genotype and subtype as well as the method used for assessment (population versus next generation sequencing). RASs can be found in any genotype or subtype, but clinical studies suggest that the baseline RASs with the greatest impact on treatment response occur in genotype 1a and 3 infections. The most important RASs are those in the NS5A protein.

NS5A RASs — Baseline RASs in NS5A are the most clinically significant. They are relatively prevalent and there are multiple different NS5A RASs, some of which impact the in vitro activity of all available NS5A inhibitors, except pibrentasvir. Nevertheless, baseline NS5A RASs have only been consistently associated with lower SVR rates in genotype 1a- and 3-infected patients being treated with an NS5A inhibitor-containing regimen [1,2,8,38]. The NS5A RASs of interest vary slightly based on the specific NS5A inhibitor and viral genotype or subtype (table 3).

- **Subtype 1a** – For patients with subtype 1a, we test for baseline NS5A RASs in patients for whom elbasvir-grazoprevir is being considered. If high level NS5A inhibitor resistance is identified in patients who are treatment-naïve or who do not have cirrhosis, we choose a regimen other than elbasvir-grazoprevir, if possible.

  Apart from planned use of elbasvir-grazoprevir, we do not test for baseline NS5A RASs in patients infected with GT1a, including those with prior treatment experience and cirrhosis. The potential benefit of this approach was limited to modifying treatment with sofosbuvir-ledipasvir; widespread availability of sofosbuvir-velpatasvir and glecaprevir-pibrentasvir have obviated the need for RAS testing in this population. (See "Management of chronic hepatitis C virus infection: Initial antiviral therapy in adults", section on 'Patients without known cirrhosis'.)

  The impact of baseline NS5A RASs has been best characterized with elbasvir-grazoprevir, and a pretreatment assessment for these RASs is recommended prior to deciding to use elbasvir-grazoprevir in genotype 1a-infected patients [39]. For those who have RASs, if elbasvir-grazoprevir is still going to be used, the regimen is given with ribavirin for 16 weeks. Baseline NS5A RASs that result in decreased activity of elbasvir (a greater than fivefold shift in the half maximal effective concentration of elbasvir) have been found by population sequencing in 5 to 10 percent of genotype 1a-infected patients [36]. Corresponding SVR rates with 12 weeks of elbasvir-grazoprevir among those with such

baseline NS5A RASs were low, ranging from 29 to 58 percent. Despite NS5A RASs being more prevalent in genotype 1b virus, no significant impact on SVR rates has been recognized with elbasvir-grazoprevir in this subtype [36].

A similar set of NS5A RASs confers in vitro resistance to ledipasvir and may impact clinical responses with ledipasvir-sofosbuvir in certain circumstances. In a combined analysis of over 2100 patients treated with ledipasvir-sofosbuvir, baseline ledipasvir RASs resulted in lower SVR rates in subtype 1a-infected patients (90 versus 98 percent without RASs) but did not substantially impact SVR rates in subtype 1b (95 versus 99 percent without RASs) [38]. The impact of baseline RASs was most pronounced when high level ledipasvir RASs (>100-fold shift; including positions M28 [except T], Q30, L31, and Y93) were present in specific subgroups:

- Patients treated for eight weeks (SVR rates 83 versus 96 percent without RASs)
- Treatment-experienced patients treated for 12 weeks with or without ribavirin (SVR rates 65 versus 97 percent without RASs)

No significant impact of baseline RASs was seen when ledipasvir-sofosbuvir was given for 24 weeks (with or without ribavirin).

Integrated analyses have not demonstrated an impact of baseline NS5A RASs on outcomes in GT1a with either sofosbuvir-velpatasvir or glecaprevir-pibrentasvir [40,41].

- **Genotype 3** – For patients with genotype 3 infection, we check for the NS5A RAS Y93H when sofosbuvir-velpatasvir is being considered for treatment-experienced patients without cirrhosis or treatment-naïve patients with cirrhosis. If present, we add ribavirin to the regimen. We routinely add ribavirin to sofosbuvir-velpatasvir for treatment-experienced patients with cirrhosis, so do not check for NS5A RASs when this regimen is planned in this population. Glecaprevir-pibrentasvir does not require treatment modification in the presence of Y93H. (See "Management of chronic hepatitis C virus infection: Initial antiviral therapy in adults", section on 'Known genotype 3 infection' and "Management of chronic hepatitis C virus infection: Antiviral retreatment following relapse in adults", section on 'Genotype 3'.)

  The prevalence of Y93H is approximately 10 percent in genotype 3 virus [1,2]. This RAS has been associated with decreased responses to both sofosbuvir-velpatasvir and sofosbuvir plus daclatasvir. For sofosbuvir-velpatasvir, SVR rates are 84 percent (versus 97 percent without Y93H) [2] and for sofosbuvir plus daclatasvir are 54 percent [1]. This RAS alone does not impact pibrentasvir activity in genotype 3 (2.3-fold shift in half maximal effective

concentration [EC50]) [42]. In an integrated analysis of patients with genotype 3 infection treated with glecaprevir-pibrentasvir, SVR12 was achieved in 91 percent of those with baseline Y93H [43].

The A30K RAS is found in 5 to 10 percent of genotype 3a viruses and confers modest in vitro resistance to velpatasvir (50-fold shift in EC50) [7,40]. While it does not confer resistance to pibrentasvir (1.1-fold shift in EC50), numerically lower response rates have been observed in its presence, particularly when glecaprevir/pibrentasvir was used for eight weeks. Among trials evaluating glecaprevir-pibrentasvir in genotype 3-infected patients, SVR rates for those with baseline A30K were 75 to 84 percent with eight weeks of treatment compared with 94 percent with 12 weeks; SVR rates were 99 percent with both durations for those without A30K [7]. Given small numbers, however, none of these differences reached statistical significance. Baseline A30K screening is not recommended [43].

NS3 RASs — In general, baseline NS3 protease inhibitor RASs do not impact treatment responses or regimen selection. Thus, there is minimal role for pretreatment screening for baseline NS3 RASs.

The only RAS found in an appreciable proportion of patients at baseline is the Q80K RAS, and it is found only in genotype 1a virus [44]. Although it decreases the in vitro potency of simeprevir (resulting in a 5- to 10-fold increase in the effective concentration that reduces viral RNA by 50 percent) [45], its clinical significance is limited as it has no in vitro impact on modern HCV NS3 PIs (grazoprevir, glecaprevir, or voxilaprevir). Simeprevir is not available in the United States and elsewhere.

Other NS3 RASs, such as at positions R155, A156, or D168, are rarely found (<1 percent) in genotype 1 virus in the absence of prior protease inhibitor exposure and thus are not clinically significant [44]. Polymorphisms at some of these key positions are found in non-genotype 1 viruses (eg, position 168 polymorphism in genotype 3) and account for the diminished activity of many currently available protease inhibitors against these other genotypes [44].

NS5B RASs — NS5B RASs are either found rarely in patients without prior NS5B inhibitor exposure or have low risk of impacting clinical outcomes. Thus, there is no role for pretreatment screening for baseline NS5B RASs.

The predominant NS5B nucleotide RAS is S282T, which has not been described in patients without previous sofosbuvir exposure [28,38]. Other polymorphisms, such as L159F and V321A, are enriched following failure with a sofosbuvir-containing regimen but do not result in

decreased sofosbuvir activity in vitro and do not appear to be associated with adverse response to retreatment [46].

Selected RASs — Limited data exist on the impact that RASs selected during failed DAA treatment have on response to subsequent therapy. The approach to patients who have failed initial DAA therapy depends on the genotype and the precise regimen that was previously used. (See "Management of chronic hepatitis C virus infection: Antiviral retreatment following relapse in adults", section on 'Regimen selection for relapse after DAA therapy'.)

The apparent impact of selected RASs differs by type of failed regimen. In one study of 41 patients who failed 8 to 12 weeks of therapy with ledipasvir-sofosbuvir and were retreated with ledipasvir-sofosbuvir for 24 weeks, the presence of ledipasvir RASs was the main predictor of response, with an SVR rate of 100 percent among the 11 patients without RASs and only 60 percent among the 30 patients with RASs [47]. Having a greater number of RASs was associated with even worse response.

In contrast, trial data on the triple DAA regimen sofosbuvir-velpatasvir-voxilaprevir did not demonstrate any impact of selected NS3 or NS5A RASs on the excellent retreatment response [16,48]. (See "Management of chronic hepatitis C virus infection: Antiviral retreatment following relapse in adults", section on 'Limited role for resistance testing'.)

Similarly, preliminary data on sofosbuvir plus glecaprevir-pibrentasvir for retreatment of patients who had failed glecaprevir-pibrentasvir did not demonstrate an impact of RASs on treatment outcomes [49].

Additionally, a number of studies evaluating the impact of selected resistance following failure with experimental, short-duration, DAA combination regimens suggest that the RAS impact is minimal on response to subsequent treatment with approved DAA regimens or more intensive three- to four-drug regimens [50,51]. This is likely because the patients failing such experimental short-course regimens are less likely to be enriched for other negative predictors (eg, cirrhosis), suggesting that selected resistance alone may not be sufficient to increase the risk of retreatment failure.

Baseline HCV RNA level — Although the baseline HCV RNA level was historically a significant factor in predicting the likelihood of response to peginterferon plus ribavirin therapy for genotype 1 infection, it has little overall impact on treatment response with DAA regimens. A modest impact of baseline viral load has been noted in select genotype 1-infected subgroups.

For treatment-naïve patients without cirrhosis who are being treated with ledipasvir-sofosbuvir, a baseline HCV RNA level <6 million international units/mL (as determined using the COBAS

Taqman HCV Test, version 2.0) allows the possibility of a shorter eight-week (rather than 12) duration [52]. In one trial of ledipasvir-sofosbuvir in treatment-naïve patients without cirrhosis, SVR rates were similar with 8 and 12 weeks of therapy (94 versus 95 percent), but rates of virologic relapse were numerically higher with 8 weeks (5 versus 1 percent with 12 weeks) [53]. In a post-hoc analysis by viral load strata, relapse rates with the two treatment durations were roughly equivalent among patients with a baseline viral load <6 million international units/mL [54]. Though the use of this cutoff has been questioned based on the lack of any statistical difference between all viral load strata [55], several real-world experiences suggest excellent response to short course therapy in this population [56,57].

In an integrated analysis of treatment-naïve genotype 1-infected patients treated with elbasvir-grazoprevir for 12 weeks, a baseline HCV RNA >800,000 international units/mL was associated with a slightly lower SVR rate (94 versus 99 percent, respectively) [8]. HCV RNA above that threshold remained a significant factor associated with nonresponse in multivariate analysis (OR 0.1, 95% CI 0.01-0.7). Despite this finding, pretreatment HCV RNA levels are not used clinically to determine treatment approaches with elbasvir-grazoprevir in the United States.

MULTIPLE NEGATIVE PREDICTORS

Given the potency and extremely high sustained virologic response (SVR) rates observed with combination direct-acting antiviral (DAA) regimens, single negative predictors have limited impact on response rates but have greater impact in combination. This is reflected in the fact that treatment modifications to optimize response are warranted only in the presence of multiple negative predictors (eg, prior treatment failure plus cirrhosis).

The impact of multiple negative predictors on treatment response has been examined with several DAA regimens. In an analysis of over 800 patients with genotype 1, 2, or 3 infection who were treated with sofosbuvir plus ribavirin (with or without interferon), negative predictors of response identified in multivariate analysis included prior treatment, male sex, weight >75 kg, non-CC IL28B genotype, cirrhosis, and HCV RNA level >800,000 international units/mL [58]. Nevertheless, the SVR rate did not drop below 90 percent until four negative predictors were present.

In a similar analysis of over 2000 genotype 1-infected patients treated with ombitasvir-paritaprevir-ritonavir plus dasabuvir with or without ribavirin (a regimen that is no longer available in the United States and elsewhere), SVR rates did not drop below 95 percent until four negative factors (including subtype 1a, weight >75 kg, being of an Hispanic/Latin American population, TT IL28B genotype, and HCV RNA level >800,000 international units/mL) were

present [59]. Of the factors considered, only elevated body mass index (BMI) and subtype 1a were independently associated with worse response.

With highly potent DAA combinations, SVR appears to remain high across multiple traditional negative predictors [60].

OBSOLETE PREDICTORS OF RESPONSE

Several clinical features that were predictors of response to interferon-based regimens are no longer relevant to combination direct-acting antiviral (DAA) regimens.

HIV coinfection — During the interferon era, HIV/HCV coinfection had been associated with significantly lower response rates compared with HCV-monoinfected patients, particularly among those with genotype 1 infection [61-63]. Response rates in HIV/HCV-coinfected patients have improved with DAA combination regimens, which result in sustained virologic response (SVR) rates nearly identical to those observed in HCV-monoinfected patients [10,24,64,65]. Recommended treatment approaches with these regimens are generally the same for coinfected and monoinfected patients but need to take into account potential drug interactions with antiretroviral agents [66]. (See "Treatment of chronic hepatitis C virus infection in the patient with HIV", section on 'Potential drug interactions with ART'.)

The lone exception to the observed efficacy equivalence may be with abbreviated eight-week treatment regimens in coinfected patients. In a study of treatment-naïve coinfected patients who received sofosbuvir plus daclatasvir, the SVR rate was only 76 percent when given for eight weeks compared with 97 percent with 12 weeks [24]. Based on this and a lack of additional clinical trial data with abbreviated treatment durations in coinfected patients, our approach is to not use eight weeks of any currently available regimen in HIV/HCV coinfected patients.

IL-28B genotype and race — Polymorphisms in the IL28B gene, which encodes interferon lambda 3, effectively predicted responses to treatment with interferon-based therapies and accounted for a significant proportion of the differential response observed in patients of certain races, such as patients of African descent [67,68]. In contrast, neither non-CC IL28B genotype nor race has consistently been associated with lower SVR rates in multiple trials and cohort studies of contemporary DAA combination regimens [69,70]. Although some studies have suggested a limited impact of IL28 genotype or race on SVR rates with DAA regimens [64,71,72], the magnitude of the impact is small when appropriate regimens are used and not sufficient enough to recommend IL28B genotype testing in routine clinical practice.

As an example, in one trial of ledipasvir-sofosbuvir for 12 weeks in HIV/HCV coinfected patients, all viral relapses occurred in Black patients, and being of a Black population was associated with a lower SVR rate (90 versus 99 percent) [64]. In contrast, in an analysis that specifically evaluated the effect of race on response among three trials of ledipasvir-sofosbuvir, this association was not replicated [69].

Likewise, an analysis of a trial evaluating 8 versus 12 weeks of ledipasvir-sofosbuvir in treatment-naïve genotype 1-infected patients without cirrhosis found an impact of IL28 genotype on outcome [71]. Among those treated for eight weeks without ribavirin, SVR rates were 98, 95, and 90 percent for those with IL28B CC, CT, and TT genotypes, respectively. However, the effect of IL28B genotype was lost when restricting analysis to those with a baseline HCV RNA <6 million copies, the population to which the eight-week regimen is restricted [52,73].

On treatment viral kinetics — On treatment HCV viral kinetics played a major role in determining treatment futility with interferon and ribavirin [74], but with the tremendous potency of combination DAA regimens, the vast majority of patients taking one of these regimens achieve an unquantifiable HCV RNA level by four weeks of therapy. Given these rapid and nearly uniform responses, no role for on treatment HCV RNA assessment has emerged to guide treatment approaches or suggest futility when combination DAA regimens are used [75,76]. Despite this, an obvious loss of virologic suppression during therapy (>1 log increase from nadir after week 4) suggests a failing regimen (eg, because of nonadherence) [77]. (See "Overview of the management of chronic hepatitis C virus infection", section on 'Viral monitoring'.)

One study had suggested a potential role for HCV RNA assessment at week two to guide therapy and determine futility in patients with genotype 1 or 3 treated with sofosbuvir plus ribavirin [76]. However, this combination is no longer a preferred regimen for either of these genotypes, which limits the clinical applicability of such an approach.

SUMMARY

- Clinical features that historically predicted worse outcomes with interferon-based regimens for chronic HCV infection have a limited impact on responses to combination direct acting antiviral (DAA) regimens. Rather than identify patients with a much lower chance of attaining cure (who thus might forgo interferon-based therapy), such features influence treatment strategies with DAA regimens, such as duration of treatment and the need for the addition of ribavirin. (See 'Introduction' above.)

- The patient and viral characteristics most pertinent to determining the appropriate HCV treatment approaches are (see 'Factors that impact regimen selection' above):

  - Presence of cirrhosis
  - History of prior HCV treatment failure

  Viral genotype played a critical role in selection of early DAA regimens, but it is less important with the widespread availability of potent pangenotypic regimens (eg, sofosbuvir-velpatasvir and glecaprevir-pibrentasvir). For certain patient populations and with certain regimens, presence of resistance-associated substitutions (RASs) also inform regimen administration. (See 'Factors that impact regimen selection' above.)

- In general, the sole presence of cirrhosis is not a major predictor of a poor response to therapy, as regimen modifications for patients with cirrhosis can yield sustained virologic response (SVR) rates that are similar to those observed patients without cirrhosis. The exception is in patients with chronic genotype 3 infection, in whom cirrhosis is the predominant feature associated with poor response to certain sofosbuvir-containing regimens, which cannot be completely overcome by extending therapy or adding ribavirin. (See 'Cirrhosis status' above.)

- The impact of prior treatment itself is modest and rarely impacts HCV treatment approaches with combination DAA regimens in the absence of other negative predictors. The key aspects in determining the impact of prior treatment are the type of prior HCV treatment (ie, peginterferon plus ribavirin, peginterferon plus ribavirin plus a DAA, or an interferon-free DAA-based regimen) and other patient characteristics, most notably the presence or absence of cirrhosis. (See 'Prior treatment failure' above.)

- Genotype 3 infection is the genotype most often associated with decreased response to treatment, particularly in the setting of cirrhosis. Nevertheless, high SVR rates can be achieved for all genotypes (including genotype 3) through optimal regimen selection and modification. (See 'HCV genotype and subtype' above.)

- RASs refer to polymorphisms that confer resistance to a particular DAA class. The prevalence of baseline RASs (present despite no prior exposure to the DAA class) varies by viral genotype and subtype. Baseline RASs appear to have the greatest impact on treatment response in genotype 3 infection, and pretreatment evaluation for RASs is recommended with certain DAA regimens for this genotype; RASs also impact response of genotype 1a infection to certain regimens that are infrequently used (table 2). Potent triple-drug combinations have obviated the need for RAS testing after DAA failure, provided these regimens are accessible. (See 'Resistance-associated substitutions' above.)

- Multiple negative predictors must be present in the same patient before an appreciably inferior SVR rate is observed. Furthermore, some features that predicted poor response to interferon-based therapy, such as HIV coinfection and non-CC IL28B genotype, are no longer associated with worse response to combination DAA therapy. Modern pangenotypic DAA regimens have further decreased the impact of negative predictors. (See 'Multiple negative predictors' above and 'Obsolete predictors of response' above.)

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Topic 16500 Version 23.0

GRAPHICS

Child-Pugh classification of severity of cirrhosis

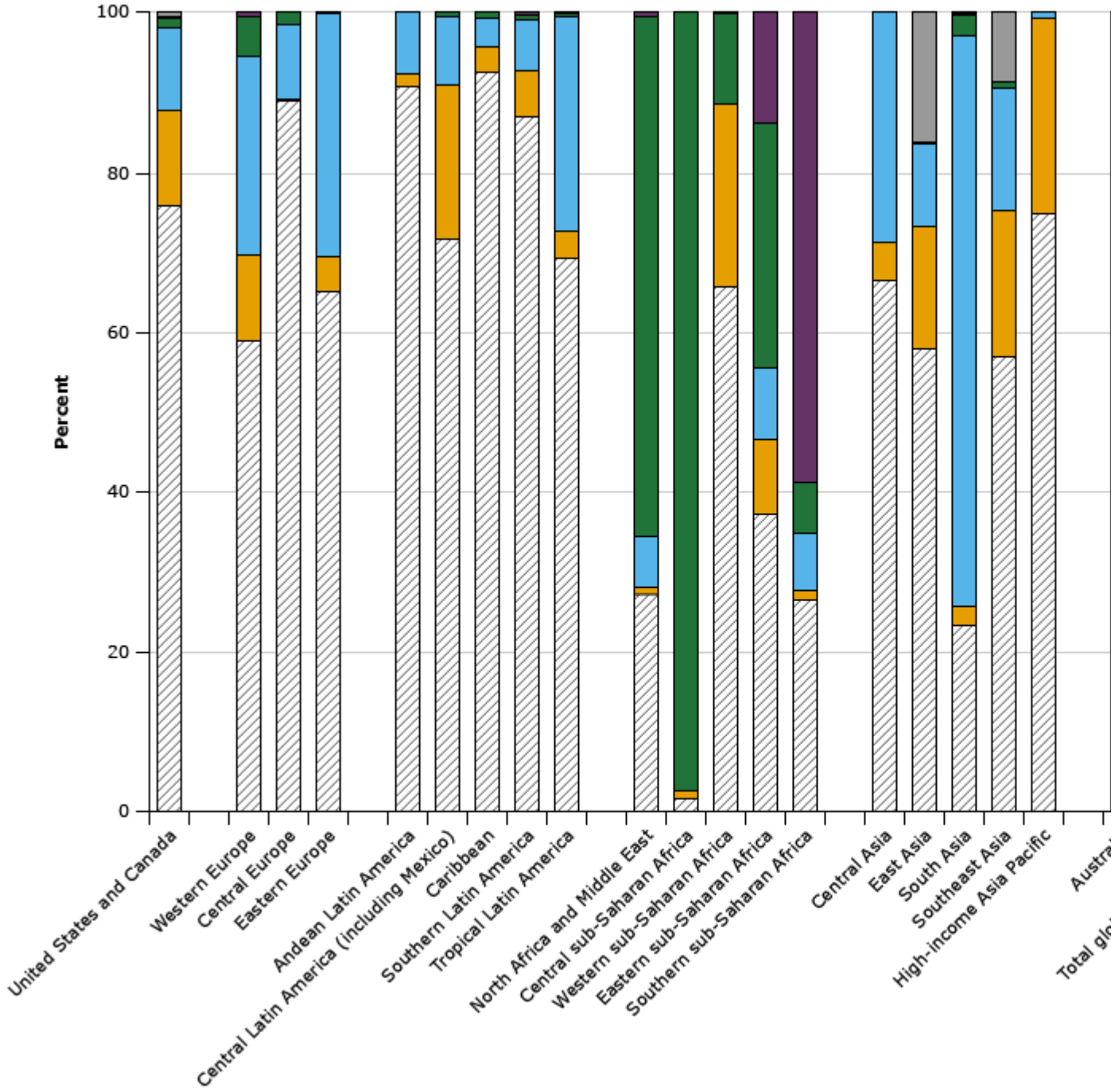
Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL (<34.2 micromol/L)	2 to 3 mg/dL (34.2 to 51.3 micromol/L)	>3 mg/dL (>51.3 micromol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8 to 3.5 g/dL (28 to 35 g/L)	<2.8 g/dL (<28 g/L)
Prothrombin time (seconds over control) or	<4	4 to 6	>6
INR	<1.7	1.7 to 2.3	>2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the serum concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total Child-Turcotte-Pugh score of 5 to 6 is considered Child-Pugh class A (well-compensated disease), 7 to 9 is class B (significant functional compromise), and 10 to 15 is class C (decompensated disease). These classes correlate with one- and two-year patient survival: class A: 100 and 85%; class B: 80 and 60%; and class C: 45 and 35%.

INR: international normalized ratio.

Graphic 78401 Version 15.0

Proportion of HCV infections caused by the six major genotypes, by geographic



HCV: hepatitis C virus

Data from: Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology 2

Graphic 99796 Version 1.0

Response to sofosbuvir-containing regimens for subtype 1a versus 1b HCV infection

Regimen	Ledipasvir-sofosbuvir (TN: 12 weeks; TE: 24 weeks)[3,4]	Sofosbuvir-velpatasvir (12 weeks)[5]	Glecaprevir-pibrentasivr (8 or 12 weeks)[6]
1a	TN: 99.3%	TN: 98% (95 to >99%)	8 weeks: 98% (94 to >99%)
	TE: 98.8%	TE: 98% (95 to >99%)	12 weeks: 99% (96 to >99%)
1b	TN: 100%	TN: 99% (95 to 100%)	8 weeks: 100%
	TE: 100%	TE: 99% (95 to 100%)	12 weeks: 100%

TE: treatment-experienced; TN: treatment-naïve.

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Resistance associated substitutions for hepatitis C virus (HCV) NS5A inhibitors

NS5A inhibitor	Genotype 1a	Genotype 3
Pibrentasvir	Y93*	No single position variants¶
Velpatasvir	Y93	Y93H
Ledipasvir	K24, M28, Q30, L31, Y93	N/A
Elbasvir	M28, Q30, L31, Y93	N/A
Daclatasvir	M28, Q30, L31, Y93	A30K, Y93H

EC50: Half maximal effective concentration

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* Results in low level resistance in vitro (<10x shift in EC50).

¶ In vitro, no single position variant results in >3x shift in EC50. Dual A30K and Y93H results in 70x shift in EC50.

Data from:

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Contributor Disclosures

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