Review

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Management of direct-acting antiviral agent failures

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Summary

Failure to respond to the approved combinations of multiple direct-acting antiviral agents is relatively low in hepatitis C virus treatment registration studies, with rates of 1% to 7%, depending on the patients' baseline characteristics. In real life, failure is slightly higher, likely because of lower compliance. Treatment failures are usually related to relapse and less often to on-treatment viral breakthrough. Hepatitis C drug-resistant variants are detected in most patients who do not achieve viral eradication. The risk of developing these variants depends on host- and virus-related factors, the properties of the drugs used, and the treatment strategies applied. Patients who carry resistance-associated variants may not obtain benefits from treatment and are at risk of disease progression and transmission of the variants. Whether hepatitis C resistance-associated variants persist depends on their type: NS3-4A variants often disappear gradually after therapy is stopped, whereas NS5A variants tend to persist for more than 2 years.

The best way to prevent emergence of resistant variants is to eliminate the virus at the first treatment using highly potent antivirals with genetic barriers to resistance. In patients failing first-generation protease inhibitors, combination therapies with sofosbuvir and NS5 inhibitors have proven effective. Some salvage regimens can be shortened to 12 weeks by addition of ribavirin. The optimal treatment for patients who fail an NS5A inhibitor and those with multidrug-resistant variants remains to be defined, and research efforts should continue to focus on treatment for these patients.

Keywords: Hepatitis C virus; Treatment; Direct-acting antivirals; Resistance-associated variants; Interferon; Sofosbuvir; Simeprevir; Daclatasvir; Ledipasvir.
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Abbreviations: HCV, hepatitis C virus; DAA, direct-acting antiviral; TPV, telaprevir; BOC, boceprevir; SMV, simeprevir; SOF, sofosbuvir; DSV, dasabuvir; LDV, ledipasvir; DCV, daclatasvir; OBV, ombitasvir; GT, genotype; RBV, ribavirin; PI, protease inhibitor; PTV/r, paritaprevir boosted with ritonavir; SVR, sustained virologic response; P, pegylated interferon; RAV, resistance-associated variant; HIV, human immunodeficiency virus; GZV, grazoprevir; EBV, elbasvir; U.S., United States; FDA, Food and Drug Administration; EMA, European Medicines Agency.

Introduction

It is estimated that 170 million people worldwide live with chronic hepatitis C virus (HCV) infection [1,2]. Most of these individuals are asymptomatic, but some experience disease progression with liver fibrosis, which can lead to cirrhosis and hepatocellular carcinoma. In 2010, more than 0.5 million deaths worldwide were attributed to infection by HCV [3].

The extraordinary recent developments in HCV treatment have completely changed the scenario of therapy for this condition. A series of new direct-acting antivirals (DAAs) against the HCV non-structural proteins have been developed, enabling incorporation of interferon-free regimens into clinical practice. These include drugs that can inhibit the NS3-4A protease, including telaprevir (TPV), boceprevir (BOC), simeprevir (SMV), and paritaprevir, agents that inhibit the NS5B polymerase, such as the nucleoside analogue, sofosbuvir (SOF), and the non-nucleoside analogue, dasabuvir (DSV), and drugs that act upon the NS5A replication complexes, such as ledipasvir (LDV), daclatasvir (DCV), and ombitasvir (OBV). Combinations of two or more of these drugs in interferon-free regimens have shown high effectiveness for viral clearance with only mild side effects. The following DAA combination regimens are currently used in clinical practice for patients infected with genotype (GT) 1 or 4 (Fig. 1): 1) SMV plus SOF ± ribavirin (RBV); 2) SOF plus an NS5A inhibitor such as DCV or LDV (the latter in a fixed-dose combination); 3) an NS3-4A protease inhibitor (PI), paritaprevir, boosted with ritonavir (PTV/r) plus an NS5A inhibitor, OBV, in a fixed-dose combination with a non-nucleoside polymerase inhibitor, DSV. This last DAA combination is also known as 3D regimen. Whichever of these regimens is used, sustained virologic response (SVR) rates in the registration studies involving GT1 or GT4 patients are higher than 90%.

The preliminary results on these DAA regimens in various real-world cohorts also show high SVR rates (80–90%), although they are slightly lower than those in the registration studies [4–12]. For patients with GT2 or GT3 infection, the first approved interferon-free regimen was SOF plus RBV for 12 to 24 weeks, which yielded SVR rates of 68% to 90% [13–16]. In addition, two DAA combinations are available for GT3: SOF plus DCV and SOF/LDV. The extensive introduction of these regimens foresees

that a fair number of patients will fail these newer antiviral treatments in the near future.

This review focusses on the management of DAA failures. We discuss the types of failures, the characteristics of patients who fail, the role of HCV drug resistance testing in this situation, and the available rescue strategies.

Key point box: Introduction

- It is estimated that 170 million people have chronic hepatitis C virus infection worldwide.
- The current standard of care therapy for chronic hepatitis C infection is a combination of direct-acting antivirals in an interferon-free regimen.
- SVR with a DAA combination in GT1 infection is above 90% in the pivotal studies and slightly lower (80%-85%) in the real-world setting.

Key point box: Failure to DAAs

- Failure to DAAs is mainly due to relapse; on-treatment virologic breakthrough is rare.
- Failure to multiple DAA regimens occurs more often in GT1a patients with cirrhosis, GT3 treatment-experienced patients with cirrhosis, and patients receiving a shorter therapy duration (<12 weeks).
- The majority of patients who fail DAA combinations harbor HCV resistance-associated variants related to the drugs used in the therapeutic regimen. NS3-4A resistance variants tend to disappear after treatment discontinuation, whereas NS5A and NS5B variants persist longer.

Key point box: Pre-treatment evaluation

- HCV drug resistance testing is not recommended in naïve patients. Sustained virologic response is similar regardless of the baseline presence of NS3-4A or NS5A resistance variants.
- Determination of the Q80K polymorphism is recommended prior to simeprevir-based therapy in genotype 1a patients.
- In patients who fail multiple DAAs, HCV resistance testing is important for deciding retreatment. Characterization of DAAs can be useful for selecting salvage therapy.

Key point box: Management of antiviral failure

- Genotype 1 patients who fail triple therapy with protease inhibitors can be retreated with the combination of sofosbuvir plus an NS5A inhibitor (daclatasvir or ledipasvir) or sofosbuvir plus simeprevir. Therapy duration of can be 12 weeks if ribavirin is added; otherwise, the recommendation is 24 weeks.
- Genotype 1 patients who fail sofosbuvir plus an NS5A inhibitor or ombitasvir/paritaprevir/r and dasabuvir may carry NS5A RAVs. The optimal salvage therapy for these patients has not been established. The current recommendation is to wait for the results of ongoing studies on combined DAAs without cross resistance or for better drugs. If there is an urgent need for retreatment, the combination of sofosbuvir plus simeprevir and ribavirin, or an interferon-based regimen may be useful.
- Genotype 3 patients who fail sofosbuvir plus ribavirin can be rescued with sofosbuvir plus daclatasvir and ribavirin for 12 to 24 weeks or sofosbuvir plus pegylated interferon and ribavirin for 12 weeks.

Treatment strategies for chronic hepatitis C

Triple therapy with first-generation NS3-4A protease inhibitors (PIs)

The NS3-4A PIs, TPV and BOC, in combination with pegylated interferon (P) and RBV were the first wave of DAAs approved for treating chronic HCV GT1, the most common HCV genotype worldwide. The efficacy of first-generation PIs depends on the viral sensitivity to interferon. Therapy failures have been reported in 20% of naïve patients and 80% of previous P/RBV null responders, particularly those with liver cirrhosis [17–24]. Patients who fail to respond to TPV harbor resistance-associated variants (RAVs) that have a profile of cross resistance to BOC and vice versa. The frequency and type of NS3-4A RAV found in patients failing TPV or BOC triple therapy depends on the HCV subtype (Table 1) [25]. These resistance variants were not detected in most patients studied after a median treatment discontinuation of 10 months in GT1a infection and 3 weeks in GT1b [26]. An important lesson regarding first-generation PIs is that RAVs quickly emerge when these drugs are administered in monotherapy; initially they are single mutations, but after continued replication, other resistant mutations may accumulate. Addition of P/RBV inhibits the growth of NS3-4A variants, suggesting that they are sensitive to P/RBV [26,27]. RBV also plays an important role in decreasing relapse and viral breakthrough, as was shown in the PROVE-2 study, where treatment failure occurred in 64% of patients receiving P/TPV and only 40% of those given P/TPV plus RBV for the same time period [17].

The NS3-4A RAVs have been detected in 8.6% of untreated GT1a and 1.4% of untreated GT1b patients [28]. However, the