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Management of Direct-Acting Antiviral Failures

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The early treatment of hepatitis C virus (HCV) with pegylated interferon (IFN) alpha and ribavirin (RBV) was fraught with serious adverse side effects and low eradication rates. Direct-acting antiviral (DAA) agents were first introduced as adjunct therapeutics for IFN and RBV therapies in the 2010s. Given their extremely low side-effect profile and their high rate of treatment success with sustained virological response (SVR) rates exceeding 95%, DAA-based regimens have now supplanted IFN and RBV as first-line treatments for HCV infection.

Three major classes of DAAs have activity against HCV, including polymerase inhibitors, protease inhibitors, and NS5A inhibitors. Treatment with DAAs leads to selection for drug-resistant variants, and the risk for treatment failure is low in patients receiving two different classes of DAAs with overlapping resistance profiles. Failure to respond to the current highly potent DAA-based regimens for HCV infection is today an uncommon occurrence in the absence of nonadherence. Nevertheless, even assuming a less than 2% failure rate, the number of patients who will need re-treatment becomes considerable given the large number of patients receiving antiviral therapy.1 It is not known, for example, whether the broad use of generics could lead to a worldwide increase in DAA treatment failures; patients with genotype 3 (GT3), especially those with cirrhosis, still represent a therapeutic challenge.

Multiple agents have been designated “DAA” over the past several years, and also there have been several trials for “DAA failures,” but currently only a select group of such compounds is used in the United States. Accordingly, there is some confusion regarding the efficacy of certain regimens for patients who previously did not respond to various regimens in the past. We encourage referencing the most current guidance document (see https://www.hcvguidelines.org/) for the most up-to-date expert guidance for a given case.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; cir, cirrhosis; Comp, compensated; DAA, direct-acting antiviral; DComp, decompensated; GEL, glecaprevir; GT, genotype; HCV, hepatitis C virus; IFN, interferon; LTFU, long-term follow-up; PIB, pibrentasvir; PTW4, posttreatment week 4; RAS, resistance-associated substitutions; SOF, sofosbuvir; SVR, sustained virological response; TF, treatment failure; Trmt, treatment; TW2, treatment week 2; VEL, velpatasvir; VOX, voxilaprevir.

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Potential conflict of interest: S.C.G. received grants from AbbVie, Conatus, Eiger, Genfit, Gilead Sciences, GlaxoSmithKline, Intercept, Merck, and Viking.

Received December 2, 2019; accepted March 23, 2020.

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The most common cause of virological failure is relapse of infection, defined as detection of viral levels after completion of treatment despite previously demonstrated clearance at the completion of therapy. Viral breakthrough is far less common and is identified during treatment when previously undetectable HCV RNA levels continue to increase. In general, clinically significant resistance to protease inhibitors is rare, whereas nonresponse to an NS5A inhibitor, with detected NS5A resistance-associated substitutions, is clinically more important. Mutations that confer resistance to NS5A inhibitors have been found in HCV variants with better genetic “fitness” and predilection for survival. Despite the heterogeneity in phenotypic expression and clinical relevance that arise from NS5A mutations, this subtype of resistance-associated substitutions (RAS) mutations may compromise SVR in patients treated with elbasvir/grazoprevir, and as such, resistance testing should be considered in GT1a patients who are planned to initiate this regimen, regardless of prior treatment status. Similarly, NS5A resistance testing is recommended prior to starting ledipasvir/sofosbuvir (SOF) for GT1a patients who are treatment experienced, and testing for Y93H specifically is suggested in subsets of GT3 patients prior to treatment with SOF/velpatasvir (VEL). The actual clinical significance of DAA failure depends on whether there was a previous nonresponse to an NS3 protease inhibitor, an NS5A inhibitor, a combination of both, or failure to respond to the newer glecaprevir/pibrentasvir (GLE/PIB) regimen.

Prior infection with HCV does not confer natural immunity, and patients remain at risk for reinfection after successful treatment. Reinfection occurs when patients are infected with a new HCV strain after previous HCV eradication and is especially germane to the discussion of HCV treatment in high-risk populations, including men who have sex with men and persons who inject drugs. Distinguishing between reinfection and treatment failure is integral to defining re-treatment regimens because reinfection poses a less complex scenario due to the lower concern for selection of viral strains with RASs.

Recognizing that DAA treatment failure represents a disparate group of patients spanning many years of evolving DAA regimens, the present summary addresses the practical approach to managing failure to achieve SVR with the currently available treatment options.

**Nonresponse to Protease or NS5A Inhibitors**

The phase 3 POLARIS trials studied the combination of SOF and VEL, inhibitors of the NS5B polymerase and NS5A, respectively, in combination with voxilaprevir (VOX), a potent NS3/4A protease inhibitor, in the treatment of HCV-infected individuals who did not respond successfully to previous treatment with DAAs. POLARIS-1 (Fig. 1) studied approximately 400 patients who did not respond positively to an NS5A inhibitor-based DAA regimen (did not include GLE/PIB) and showed that 12 weeks of SOF/VEL/VOX resulted in SVR rates that exceeded 95% across all GTs, including those with compensated cirrhosis. The six patients who relapsed after this regimen were all GT3. This regimen was found to be similarly effective in patients with and without cirrhosis who were previously treated with DAA regimens that included NS5A inhibitors.

POLARIS-4 (Fig. 2) studied 333 DAA-experienced patients but excluded patients who had received an NS5A inhibitor. Patients were randomized to receive 12 weeks of either SOF/VEL or SOF/VEL/VOX. The SOF/VEL/VOX regimen achieved SVR in 97% versus 90% in the SOF/VEL group, but the difference was only statistically significant in patients infected with GT1a and GT3. Therefore, this triple-DAA regimen, albeit costly, offers a highly effective option for most patients with HCV who did not achieve SVR with previous DAA regimens (excluding those patients with cirrhosis who have ever, at any time, developed decompensation).
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GLE/PIB Failures

The POLARIS trials for DAA failures were performed before the availability of the GLE/PIB regimen; therefore, a major data clinical gap exists regarding how to manage GLE/PIB failures. This combination therapy pairing a highly potent NS3/4A protease inhibitor and a NS5A was US Food and Drug Administration approved in 2017 for use not only in treatment-naive patients, but also in patients previously treated with either NS5A inhibitor or an NS3/4A protease inhibitor. Failure to respond to the GLE/PIB regimen therefore infers that such patients should ideally receive retreatment with a backbone that includes the NS5B SOF. The MAGELLAN-3 trial4 (Fig. 3) explored the combination of GLE/PIB, SOF, and weight-based RBV as treatment for patients who had virological failure after treatment with GLE/PIB (many of these patients had received other regimens before nonresponse to GLE/PIB). A 12-week course of SOF/GLE/PIB/RBV resulted in SVR among two GT2 patients without cirrhosis who had received no prior treatment before unsuccessful response to GLE-PIB. Among the remaining 21 patients, including patients with compensated cirrhosis and patients who had previously received NS5A or NS3/4A protease inhibitors, a 16-week course of SOF/GLE/PIB/RBV proved highly successful (95% SVR) with only one relapse. The patient who relapsed was a white man with compensated cirrhosis who had multiple previous unsuccessful regimens and had multiple complex NS3- and NS5A-resistant substitutions, including NS5A Q30K+Y93H prior to treatment and NS3 A156V at relapse in MAGELLAN-3. The patient was undetectable at treatment week 2 (TW2) and experienced relapse at posttreatment week 4 (PTW4).

Accordingly, the GLE/PIB/SOF/RBV regimen offers an attractive rescue option for the rare patient who does not respond successfully to GLE/PIB and should be offered before any signs of decompensation ensue.

Another option for GLE/PIB failure was recently reported by Pearlman et al.5 Among 31 patients with previously unsuccessful GLE/PIB regimens who were treated with SOF/VEL/VOX for 12 weeks, 29 (94%) achieved SVR. The two patients who experienced relapses included one with GT1 with cirrhosis and one with GT3 without cirrhosis.

From these two trials, therefore, the GLE/PIB/SOF/RBV regimen for 16 weeks or the SOF/VEL/VOX regimen for 12 weeks should be considered for the patient who does not respond successfully to GLE/PIB. In addition, SOF/VEL/VOX+RBV is an attractive option that is recommended in compensated cirrhosis.
ROLE OF RBV

The limited recent literature that studied RBV prospectively suggests that there remains a role for weight-based RBV in certain settings (such as in the patients with decompensated cirrhosis). Although RBV was not studied systematically among patients who experienced DAA treatment failure, a recent retrospective analysis of US patients found that the addition of RBV (versus no RBV) improves SVR among patients with previous DAA treatment failure (adjusted odds ratio [aOR], 5.43) (Fig. 4). This study also showed that adjuvant RBV (versus no RBV) improves SVR among GT3 patients (aOR, 13.28). Given that patients who did not respond successfully to DAA treatment represent such a difficult clinical dilemma, and inasmuch as no options exist for the patients who subsequently do not respond positively to these salvage therapies, consideration should be given to the adjuvant use of weight-based RBV in such settings.

SUMMARY

A small but not insignificant proportion of patients remain nonresponsive to even the current potent DAAs and experience virological failure. Patients with unsuccessful prior NS3/4A or NS5A inhibitors treatment can be treated with SOF/VEL/VOX for 12 weeks. Two SOF-based regimens are available to treat patients with previously unsuccessful GLE/PIB treatment. When feasible, the addition of RBV for the management of DAA failures can be considered. Even with these salvage regimens, however, some patients will not be cured of this chronic viral infection.

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