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Management of Hepatitis C Treatment Failures Following Direct Acting Antiviral Therapy: Review Article

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ABSTRACT

Background: Around 50 million people worldwide have Hepatitis C virus (HCV) infection, suggesting its significant public health impact. Direct-acting antiviral agents (DAAs) have revolutionized HCV treatment, resulting in high sustained virological response rates (SVR). A small but considerable minority of patients fail to achieve SVR, which is a major issue. This issue is especially important when non-structural protein 5A (NS5A) inhibitor-based therapies fail. This requires the best management practices. **Objectives:** This review article aimed to outline the current recommendations for retreatment of HCV infection after prior unsuccessful DAAs therapy.

Methods: The terms Hepatitis C virus, Direct-acting antivirals and DAA treatment failure were used to search PubMed, Science direct and Google scholar. Additionally, the writers culled references from the pertinent literature, identifying and included just the most current or comprehensive study out of all the found studies and reviews. The search for literature was limited to English language works. Dissertations, oral presentations, conference papers, unpublished articles, and abstracts from smaller scientific investigations were excluded.

Conclusion: The 12-week treatment plan of sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) is the main approach for treating instances of HCV that did not achieve SVR after previous treatments containing NS5A inhibitors and/or protease inhibitors. Nevertheless, for individuals with liver cirrhosis and genotype 3, the inclusion of ribavirin (RBV) or prolonging the duration of treatment to 24 weeks could potentially be advantageous. On the other hand, individuals who have previously undergone repeated DAA therapy may need to undergo retreatment with either a combination of SOF/VEL/VOX or a combination of sofosbuvir, glecaprevir, and pibrentasvir together with ribavirin for a duration of 16-24 weeks. Additionally, persons suffering from decompensated liver cirrhosis should have a second round of treatment using the SOF/VEL/RBV combination for a duration of 24 weeks. The multi-targeted DAA treatment strategy represents an effective anti-HCV rescue therapy for post DAAs treatment failures, although a minority of cases will remain in need for more advanced therapeutic options.

Keywords: Hepatitis C virus, Direct-acting antivirals, DAA treatment failure.

INTRODUCTION

Approximately 50 million individuals globally are infected with hepatitis C virus (HCV) with about one million new cases are reported annually, making it a critical global health concern. In 2022, there were approximately 242,000 documented deaths primarily due to cirrhosis and primary liver cancer resulting from chronic HCV infection [1].

Recent data from one of the largest disease screening campaigns ever conducted, implemented in Egypt and involving over 49 million citizens, revealed HCV antibody positivity rate of 4.61%, with 76.5% of those individuals having active viremia. The sustained virological response (SVR) achieved among treated patients during this unprecedented campaign was exceptionally high, with more than 98% of patients with known treatment outcomes reaching SVR [2].

The primary objective of HCV treatment is to achieve an SVR, defined as the absence of detectable viral ribonucleic acid (RNA) at 12 weeks (SVR12) or 24 weeks (SVR24) post-treatment. The concordance between outcomes at these two time points exceeds 99%. Long-term studies have confirmed that achieving SVR is equivalent to a definitive cure of the viral infection [3].

Direct-acting antiviral agents (DAAs) have significantly enhanced the efficacy of HCV treatment. The adoption of all-oral, interferon-free DAA regimens has resulted in impressive SVR rates, excellent tolerability, and shorter treatment durations. These advancements suggest that the global elimination of HCV is a feasible objective [4]. Even in the modern era of DAAs, HCV genotyping and subtyping are still critical for determining the best treatment strategy. This is owing to variances in treatment response rates among DAA combinations, as well as the prevalence/evolution of drug-resistant HCV variants, even for DAAs with well-established broad spectrum or pan-genotypic antiviral properties [5].

Nevertheless, it may be feasible to treat all chronic HCV patients using pan-genotypic regimes without genotyping/subtyping. This is especially useful when these tests are unavailable or more expensive than the

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antiviral medications, or to simplify and improve treatment as well as patient access to care [6].

HCV TREATMENT FAILURE

A small yet significant proportion (1-15%) of hepatitis C patients who get treatment experience treatment failures, meaning they do not achieve SVR. These failures can be attributed to numerous variables that may be connected to the host, virus, or drugs used in treatment. The most major factor leading to treatment failure is the development of viral resistance. Although this incident is rather rare, it nonetheless presents a difficult scenario [7, 8].

Of the important host-related factors influencing HCV treatment outcomes are the presence of advanced liver fibrosis or cirrhosis and male sex as well as null responders to previous anti-HCV therapy being linked to significantly lower treatment success rates [9]. Whereas virus and drug-related factors predisposing to treatment failure have a considerably greater impact on response to DAAs therapy. An important factor is the development of viral resistance to HCV resistance-associated substitutions (RASs). RASs refer to the amino acid changes that increase viral resistance, while resistance-associated variants (RAVs) are HCV variants that have lower susceptibility to DAAs and include those substitutions [3].

Regardless of the HCV genotype, DAA-RAVs are highly prevalent worldwide (up to 58.7%), where RAVs to protease inhibitors (PIs) are the most frequent, followed by those to non-structural protein 5A (NS5A) inhibitors (40.0% and 29.6%, respectively), while RAVs to nucleoside polymerase inhibitors being much less common (4%). Fortunately, the simultaneous presence of multiple RAVs to the suggested DAA regimen is extremely uncommon [10].

MANAGEMENT OF HCV TREATMENT FAILURE

Treatment failure following anti-HCV DAA medications can be hard to manage, particularly when virological failure follows NS5A inhibitor-based regimens. Approximately 10-50% of patients who are new to treatment will naturally develop NS5A inhibitor-specific RASs. However, when an NS5A inhibitor-containing therapy is unable to produce a cure, over 75% of patients will develop NS5A-specific RASs. Regretfully, these NS5A inhibitor-selected RASs continue to exist even 96 weeks after the completion of an ineffective treatment, which raises the risk of further treatment failure [11, 12].

Using a combination of different DAA classes with sofosbuvir (SOF) as the cornerstone of the antiviral regimen and extending the treatment duration (e.g., 24 weeks) with or without the addition of ribavirin (RBV) to overcome the underlying causes of treatment failure like viral resistance is one suggested strategy to manage treatment failure after previous DAAs [12].

Interestingly, pre-treatment RASs assessment is unnecessary for HCV genotypes 1b, 2, 4, and 6 given the existence of baseline RASs don't appear to impact treatment outcome. Yet on the other hand, pre-treatment RASs assays are useful for certain DAA regimens in particular patient subgroups, for example RASs might alter treatment choice in patients with HCV genotype 1a and possibly genotype 3 [13].

THE EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL) RECOMMENDATIONS:

Patients diagnosed with chronic HCV who did not achieve SVR following previous DAA medication should undergo retreatment. The retreatment should be conducted by a multidisciplinary team comprising therapists and virologists who possess expertise in the treatment of HCV. If testing for RAVs is not possible, the decision-making process for salvage therapy should rely on identifying the previously ineffective DAAs utilized, or alternatively, should be informed by the stated likelihoods of treatment response as indicated by the findings of resistance profiling [14].

Patients with HCV, regardless of whether they have compensated liver cirrhosis or not, who did not achieve a cure after previous treatment with DAA regimens containing PI or NS5A inhibitors, should be treated again with a combination of SOF plus velpatasvir and voxilaprevir (SOF/VEL/VOX) for a period of 12 weeks [14]. The well-established effectiveness of this co-formulated single tablet SOF/VEL/VOX triple combo, along with the high achieved SVR rates in multiple real-world studies irrespective of HCV genotype, patient gender, or baseline viral load, make it the treatment of choice for managing HCV after DAAs treatment failures [15-17].

In patients with a decreased likelihood of response, characterized by advanced liver disease, multiple prior DAA failures, or complex baseline RAS patterns for NS5A inhibitors, a combination of SOF and glecaprevir/pibrentasvir (GLE/PIB) for 12 weeks, following a multidisciplinary team discussion, may be a viable option [14].

A more challenging scenario involves patients who have failed two or more DAA courses that included a PI and/or NS5A inhibitor. For these exceptionally difficult-to-treat patients, a multidisciplinary team might recommend salvage therapy consisting of SOF/VEL/VOX or SOF/GLE/PIB, supplemented with weight-based RBV (1000 mg for patients under 75 kg or 1200 mg for those over 75 kg), and/or extending the treatment duration to 16 or 24 weeks. The triple combination of SOF/GLE/PIB for 24 weeks with the

addition of weight-based RBV should be offered as rescue therapy for managing failures after SOF/VEL/VOX therapy. On the other hand, patients with decompensated liver cirrhosis i.e. Child-Turcotte-Pugh (CTP) class B or C, who did not achieve SVR following regimens containing PIs or NS5A inhibitors are not eligible candidates for regimens involving PIs, hence should get treated with SOF/VEL/RBV combination for 24 weeks while being closely monitored in centers with special expertise and easy access to liver transplantation [14].

THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES (AASLD) RECOMMENDATIONS:

Generally, patients with or without compensated cirrhosis who have experienced HCV treatment failure after using SOF-based regimens (such as SOF/VEL, SOF/RBV ± interferon (IFN), and SOF/ledipasvir) or Grazoprevir/Elbasvir (GZR/EBR) can be effectively retreated with a 12-week course of the SOF/VEL/VOX triple combination. An important exception to this approach applies to HCV genotype 3 patients with liver cirrhosis. For these patients, it is recommended to add RBV to the combination therapy for the same 12-week duration, if they are eligible. For those ineligibles for RBV, extending the treatment duration to 24 weeks is advised [18-20]. Additionally, the fixed-dose combination of GLE/PIB for 16 weeks offers a potential alternative for retreatment after failure of DAA therapy. However, this alternative may not be suitable for patients who have previously been treated with regimens containing both an NS5A inhibitor and a protease inhibitor (e.g., GZR/EBR) or for those with HCV genotype 3 who have prior experience with SOF/NS5A inhibitors [18,21,22]. In cases of previous GLE/PIB treatment failure, whether or not the patient has compensated cirrhosis, the following combinations should be considered: SOF/GLE/PIB/RBV for 16 weeks or SOF/VEL/VOX for 12 weeks. For patients with liver cirrhosis, adding weight-based ribavirin (RBV) might be beneficial [18,23,24].

In view of the limited available data about management of heavily DAA-experienced patients who suffered of multiple failures of DAA regimens including those with prior SOF/VEL/VOX or SOF/GLE/PIB experience, the suggested rescue therapy could be either a combination of SOF/GLE/PIB/RBV for 16 weeks, or SOF/VEL/VOX/RBV for 24 weeks. While many patients might benefit from such novel rescue treatment with "multiple targeted therapies", some others will remain in need for more advanced therapeutic options [18,25,26]. In cases of HCV genotype 3 infection with liver cirrhosis and treatment non-responders after using the SOF/GLE/PIB regimen, it may be worth considering extending the combination therapy to 24 weeks or possibly longer [18,23].

The majority of HCV-infected patients with decompensated cirrhosis (CTP class B or C) who received DAA therapy experience significant clinical and biochemical improvement, and some were even removed off transplantation waiting lists. However, it is possible that this alone may not be enough to completely reduce the overall risk of liver-related illness, death, or the necessity for a liver transplant. This underscores the reality that not all patients with decompensated liver cirrhosis will experience positive outcomes following therapy with DAAs. Although the factors that determine improvement or deterioration are not well-defined, patients with a Model for End-Stage Liver Disease (MELD) score exceeding 20 points or those experiencing severe portal hypertensive consequences are less likely to show improvement after receiving antiviral therapy. These patients may benefit more from liver transplantation [27,30].

In chronic hepatitis C patients with decompensated cirrhosis, administration of antiviral therapy should be under close supervision of experienced hepatologist in such cases preferably in a liver transplantation facility. Furthermore, until further satisfactory data are available about safety and tolerability of PIs (e.g GLE, VOX, GZR) use in case of decompensated liver cirrhosis (CTP Class B or C), this class of DAAs should be avoided in patients with moderate or severe hepatic impairment [18].

The recommended re-treatment regimen for HCV-infected patients with decompensated cirrhosis (all genotypes), including those awaiting liver transplantation and those with hepatocellular carcinoma, who have previously failed SOF or NS5A inhibitor-based regimens, is a combination of SOF/VEL and weight-based ribavirin RBV for 24 weeks. For patients with CTP class C liver cirrhosis, it is advised to start RBV treatment at a low dose of 600 mg per day, gradually increasing the dosage if well tolerated. Patients ineligible for RBV can be re-treated with SOF/VEL alone for 24 weeks. However, further research with larger sample sizes is necessary to determine the optimal treatment duration [18,31].

For patients with decompensated liver cirrhosis (CTP Class B or C) who have previously failed a SOF-based regimen, a 24-week treatment combining SOF, ledipasvir, and RBV is recommended as a salvage therapy for HCV genotypes 1, 4, 5, or 6 [18, 32].

Due to the limited data on the treatment of mixed-genotype HCV infections (e.g genotypes 1a and 2), the use of a pan-genotypic DAA combination is preferred. In cases where the optimal DAA combination or treatment duration is uncertain, professional medical advice should be sought [18].

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