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# Update on Recommendations for the Clinical Management of Hepatitis C in Iran 2017

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## 1. Background

Treatment of the hepatitis C virus (HCV) has greatly transformed through recent decades (1). Nowadays, the HCV infection is a curable disease with introduction of HCV direct-acting antiviral (DAA) agents (2-4). Since 2015, various all-oral regimens approved for treatment of HCV with introduction of new treatment regimens in 2017 including sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) and glecaprevir/pibrentasvir (GLE/PIB). Hopefully, the generic DAAs including SOF, sofosbuvir/ledipasvir fixed dose combination (SOF/LDV), daclatasvir (DCV) and sofosbuvir/daclatasvir fixed dose combination (SOF/DCV) are available in Iran since 2016 (5, 6). With availability of these generic DAAs, Iranian healthcare system decided to eliminate hepatitis C in the country with an estimation of 186000 infected patients (7, 8). It has been estimated that 4500 patients with the HCV infection were treated for HCV in 2015 and the number of treated patients increased to 6200 in 2016 (based on the unpublished data). The number of treatment uptakes should increase to 18000 in 2018 - 2030 annually to achieve the goal of HCV elimination in Iran by 2030 (8).

In 2016, Iran hepatitis network (IHN) prepared the "Recommendations for the Clinical Management of Hepatitis C in Iran: A Consensus-Based National Guideline" based on the availability of evidences and generic DAAs in Iran (9). However, based on the rapid evolution of the published evidences in literature and also availability of new treatment regimens, there is a great need to update the treatment protocol in Iran. Moreover, with treating more than 12000 cases with SOF/LDV or SOF/DCV or SOF + DCV in 2015 - 2017, it is expected to observe more than 300 cases of treatment failure, which they need retreatment with another regimen. Hopefully, the new treatment regimen of sofosbuvir/velpatasvir fixed dose combination (SOF/VEL) is now available as a generic drug in Iran. In this editorial we decided to present an update on recommendations for the clinical management of hepatitis C in Iran.

## 2. Update on Treatment of HCV Genotype 1 and 4 Infections

Recent real-world studies on treatment of HCV genotype 1 (HCV-1) infection demonstrated that 12 weeks of SOF/LDV, SOF + DCV or SOF/VEL is efficient for treatment of the HCV-1 infection in non-cirrhotic patients without previous history of HCV antiviral therapy (2, 5, 10-12). Treatment with suboptimal regimen of SOF + Pegylated Interferon (PegIFN) + RBV with around 90% efficacy in HCV-1 is not recommended anymore (3). In HCV-1 infected patients with a previous history of PegIFN + RBV therapy and/or cirrhosis (child A), intensification of 12 weeks of SOF/LDV or SOF + DCV with adding RBV is recommended, however, the latter groups can be treated with 12 weeks of SOF/VEL without addition of RBV (2, 11, 12). Moreover, decompensated cirrhosis (child B and C) patients with HCV-1 infection can be treated for 24 weeks of SOF/LDV, SOF + DCV or SOF/VEL with addition of RBV (4, 6, 11, 13). However, in RBV-intolerant cases, treatment can be extended to 24 weeks of SOF/LDV, SOF + DCV, or SOF/VEL without RBV. Based on the availability of SOF/VEL in Iran, HCV-1 infected patients with a history of IFN-free DAA-therapy can be retreated with 24 weeks of SOF/VEL with addition of RBV and around a 95% chance of treatment success (14). The recommendations for treatment of HCV-G1 and -G4 are summarized in Table 1.

## 3. Update on Treatment of HCV Genotype 3 Infection

Non-cirrhotic, treatment naïve patients with HCV-3 can be treated with 12 weeks of SOF + DCV or SOF/VEL (11, 15). Treatment of non-cirrhotic HCV-3 infected patients with history of PegIFN + RBV therapy should be intensified by

**Table 1.** Treatment of Patients with Hepatitis C Virus Genotype 1 and 4 Infections

| Treatment Naïve Patients without Cirrhosis | DAA-naïve Patients with Compensated Cirrhosis[a] (Child A) and/or History of PegIFN+RBV Therapy | DAA-naïve Patients with Decompensated Cirrhosis (Child B or C) | DAA-experienced Patients |
|---|---|---|---|
| A. Daily DCV (60 mg) + Daily SOF (400 mg) for 12 weeks | A. Daily DCV (60 mg) + Daily SOF (400 mg) with Daily RBV (1000-1200 mg) for 12 weeks[b] | A. Daily DCV (60 mg) + Daily SOF (400 mg) with Daily RBV (1000-1200 mg) for 24 weeks[b] | A. Daily VEL (100 mg) + Daily SOF (400mg) with Daily RBV (1000-1200 mg) for 24 weeks[b] |
| B. Daily LDV (90 mg) + Daily SOF (400mg) for 12 weeks | B. Daily LDV (90 mg) + Daily SOF (400mg) with Daily RBV (1000-1200 mg) for 12 weeks[b] | B. Daily LDV (90 mg) + Daily SOF (400mg) with Daily RBV (1000-1200 mg) for 24 weeks[b] | |
| C. Daily VEL (100 mg) + Daily SOF (400 mg) for 12 weeks | C. Daily VEL (100 mg) + Daily SOF (400 mg) for 12 weeks | C. Daily VEL (100 mg) + Daily SOF (400mg) with Daily RBV (1000-1200 mg) for 24 weeks[b] | |

Abbreviations: DCV, daclatasvir; LDV, ledipasvir; PegIFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir.
[a] Including patients with pre-cirrhosis (F3 - F4).
[b] 24 weeks without RBV in cases with RBV intolerance or contraindication.

adding RBV to 12 weeks of SOF + DCV or SOF/VEL (15, 16). Cirrhotic (child A) patients with HCV-3 infection should be treated with 24 weeks of SOF + DCV + RBV and 12 weeks of SOF/VEL+RBV (15, 16). Furthermore, decompensated cirrhosis (child B and C) patients with HCV-3 infection should be treated 24 weeks of SOF + DCV or SOF/VEL with addition of RBV (13, 16). However, in RBV-intolerant cases, treatment can be extended to 24 weeks of SOF + DCV or SOF/VEL without RBV. Based on the availability of SOF/VEL in Iran, HCV-3 infected patients with history of IFN-free DAA-therapy can be retreated with 24 weeks SOF/VEL with addition of RBV and around a 80% chance of treatment success (14). The recommendations for treatment of HCV-G3 are summarized in Table 2.

## 4. Is it Important to Genotype HCV Prior to Treatment?

For around 20 years, HCV genotyping was the routine laboratory evaluation prior to initiation of HCV treatment with IFN-based therapies. Patients with HCV-1 were classified as "hard-to-treat" and needed intensified treatment with IFN-based treatments in terms of treatment duration. On the other hand, patients with HCV-3 needed a shorter therapy duration and achieved a higher rate of treatment success with IFN-based therapies than patients with HCV-1 infection (17, 18). With introduction of DAAs the role of HCV genotyping in clinical management of hepatitis C has been faded. With availability of SOF + DCV regimen in Iran, patients with HCV infection could be treated with this regimen without the result of HCV genotyping, however, if the HCV-3 infected patients harbor cirrhosis, they would need an intensified therapy using 24 weeks of SOF + DCV + RBV (Table 2). With availability of SOF/VEL regimen in Iran, it seems that HCV genotyping can be excluded from the clinical management of HCV infection if we add RBV to treatment of all patients with cirrhosis and/or previous history of treatment with PegIFN + RBV.

## 5. Update on Treatment of HCV in Patients with Chronic Renal Failure

Patients with renal failure or on hemodialysis are at a higher risk for HCV infection and therefore, treatment of these patients needs special attention. The best strategy for these patients without liver cirrhosis is sending them to renal transplantation. Treatment of HCV infection should be postponed to 3 months after transplantation (19). According to the guidelines "timing of HCV treatment in relation to kidney transplantation (before vs. after)" should be based on donor type (living vs. deceased donor), waitlist times by donor type, center-specific policies for using kidneys from HCV-infected deceased donors, HCV genotype, and severity of liver fibrosis. In non-cirrhotic patients, that are Metavir F0 - F3, kidney transplant candidacy and graft access should dictate timing of therapy. The drug interactions, to be mindful of significantly increased Cmax Simeprevir (SMV) with cyclosporine, significantly increased calcineurin inhibitor levels with SMV and DSV/OBV/PTV/ritonavir and the protease inhibitors with antifungals. In Iran, we do not have access to the latter DAAs and there are no significant interactions with the available HCV antiviral regimen in Iran. Patients with both decompensated liver disease and end-stage renal disease (ESRD) who are considered transplant candidates must be listed for a combined liver/kidney transplant. Antiviral therapy in this setting should be postponed to the post-transplant setting.

Recently, renal safety of new DAA regimens in HCV patients with comorbid ESRD is clear. The FDA has not

**Table 2.** Treatment of Patients with Hepatitis C Virus Genotype 3 Infection

| Treatment Naïve Patients without Cirrhosis | DAA-naïve, PegIFN+RBV-experienced Patients without Cirrhosis | DAA-naïve Patients with Cirrhosis[a] (Child A) ± History of PegIFN+RBV Therapy | DAA-naïve Patients with Decompensated Cirrhosis (Child B or C) | DAA-experienced Patients |
|---|---|---|---|---|
| A. Daily DCV (60 mg) + Daily SOF (400 mg) for 12 weeks | A. Daily DCV (60 mg) + Daily SOF (400 mg) with Daily RBV (1000-1200 mg) for 12 weeks[b] | A. Daily DCV (60 mg) + Daily SOF (400 mg) with Daily RBV (1000-1200 mg) for 24 weeks[b] | A. Daily DCV (60 mg) + Daily SOF (400 mg) with Daily RBV (1000-1200 mg) for 24 weeks[b] | A. Daily VEL (100 mg) + Daily SOF (400mg) with Daily RBV (1000-1200 mg) for 24 weeks[b] |
| B. Daily VEL (100 mg) + Daily SOF (400 mg) for 12 weeks | B. Daily VEL (100 mg) + Daily SOF (400 mg) with Daily RBV (1000-1200 mg) for 12 weeks[b] | B. Daily VEL (100 mg) + Daily SOF (400 mg) with Daily RBV (1000-1200 mg) for 12 weeks[b] | B. Daily VEL (100 mg) + Daily SOF (400 mg) with Daily RBV (1000-1200 mg) for 24 weeks[b] | |

Abbreviation: DCV, daclatasvir; PegIFN, pegylated interferon; RBV, ribavirin; SOF, ledipasvir; VEL, velpatasvir.
[a]Including patients with pre-cirrhosis (F3-F4).
[b]24 weeks without RBV in cases with RBV intolerance or contraindication.

yet approved SOF-based therapy, however, in Iranian experiences (Unpublished), these patients tolerated SOF + DCV and SOF/LDV therapies. Nonetheless, this limited data evaluating SOF-based regimens is inadequate to provide stronger guidance on its potential role in clinical practice. We need to multicenter cohort studies. Unfortunately, DSV/OBV/PTV/ritonavir cannot be administered in advanced liver diseases and Grazoprevir/Elbasvir regimen is not available in Iran.

In conclusion, with this update on clinical management of HCV infection in Iran, the treatment strategy is more feasible and less complex than before and more HCV patients can uptake treatment with active patient finding and integration of HCV treatment in primary public health system. The patients with failure following IFN-free DAA regimens can be treated in liver-specialized clinics using intensified SOF/VEL regimen.

## Footnotes

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