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Editorial

New Promsing Treatment Strategy for Hepatitis C Patients in 21 Century

Mohammad Sadik Memon* and Madiha Zaki
Gastroenterologist and Hepatologist, Asian Institute of Medical Science, Pakistan

***Corresponding author:** Mohammad Sadik Memon, Gastroenterologist and Hepatologist, Asian Institute of Medical Science, Pakistan, Tel: 92-22-2030161-70, Ext: 2312, 2337); Fax: +92222030432; Email: sadikmemon@gmail.com

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Hepatitis C has been called a silent epidemic: An estimated 130–170 million people are infected with hepatitis C worldwide leading to significant morbidity, mortality, and financial burden on healthcare [1] Most of them have no knowledge of their infection or of the ensuring hepatic condition, the condition can lead to the development of cirrhosis and liver cancer, and is the leading indication for liver transplantation. Many countries in worldwide including Pakistan faces dramatic increase rate of HCV infection. Despite aggressive programs toward education, care, and treatment over the last 10 years, Pakistan faces the largest burden of HCV infection in the world. The treatment of hepatitis C is complex and time-consuming. Anti HCV therapies require multiple modes of administration, can have numerous side effects, and require careful monitoring of symptoms and laboratory tests. Treatment complexity is further exacerbated by co morbid conditions that are more prevalent among HCV-infected patients, including mental health disorders (e.g., depression) and addictions (e.g., to alcohol and drugs). The landscape of antiviral treatment for hepatitis C is changing rapidly. Until recently, the standard therapy was the combination of peginterferon-alpha (PEG-IFN) and ribavirin (RBV), in all genotypes including 3 which are most prevalent in Pakistan. Usually administered for 48 weeks in patients with genotype 1, 4, 5 and 6, and 24 weeks in those with genotypes 2 and 3 [2]. In the pivotal clinical trials for registration of pegylated IFN-a and ribavirin therapy, SVR was achieved in 46% and 42% of patients infected with HCV genotype 1 treated with pegylated IFN-a2a or pegylated IFN-a2b and ribavirin [3,4], 75% to 85% in patients with genotype 2 or genotype 3 respectively [5,6]. The approval of two hepatitis C virus (HCV) protease inhibitors by the U. S. Food and Drug Administration in 2011--boceprevir and telaprevir--marked the start of a new chapter in hepatitis C treatment. With boceprevir and telaprevir, triple combination therapy for patients with genotype 1 HCV infection became available, combining peginterferon and ribavirin with either of these two agents. This represented a huge advance in hepatitis C treatment, with improved Sustained Viral Response (SVR) rates among patients who had never been treated before as well as among patients who had relapsed after treatment or did not fully respond to standard treatment [7,8]. SVR rates among treatment-naïve patients were ~70% in TELAPREVIR-INCLUDED REGIMENS [9,10]. The SVR rates among patients with no previous response were 30~40% and those among patients with a previous relapse were 70~75%, both in telaprevir-included regimens [11]. The addition of BOCEPREVIR to SOC results in higher SVR rates in both treatment-naïve and re-treated patients infected with HCV genotype 1 [12]. SVR rates were significantly higher in boceprevir-included regimens than in SOC among patients who had a prior relapse (69-75% vs. 29%) or a prior non responder (40-52% vs. 7%) [13]. several other new agents and combinations of agents are approved in 2014-2015, making several new treatment regimens available for patients.

All of these new drugs are called "DAAs"--direct acting antivirals. There are four major different HCV DAA classes:

- HCV NS3/4 Protease Inhibitors
- Nucleos(t)ide HCV NS5B Polymerase Inhibitors
- Non-nucleos(t)ide HCV NS5B Polymerase Inhibitors
- HCV NS5A Inhibitors

Interferon-free treatment: combining DAAs with each other and/or with ribavirin, for regimens which do not use interferon at all and are "interferon-free." it is most important to realize that many DAAs have been showing Phase 2 and Phase 3 trials with increased SVR rates, shortened durations of treatment, and acceptable adverse event profiles, creating intriguing possibilities for patients who have not been candidates for hepatitis C treatment because of the toxicities caused by interferon. Of importance is an interferon-sparing combination that might potentially be used in all patients who cannot use interferon such as subjects with decompensated cirrhosis or low platelet count [14]. SOFOSBUVIR (GS-7977/PSI-7977) is a nucleotide inhibitor of HCV NS5B polymerase is the most preferred drug in HCV treatment now. Triple therapy including peginterferon plus ribavirin and sofosbuvir cures >90% of patients treated for 12 or 24 weeks regardless of HCV genotype [15]. This drug is now available in Pakistan however its cost is four times more than other less effective drugs for HCV in Pakistan. Daclatasvir (BMS-790052) was the first NS5A inhibitor reaching clinical evaluation. Daclatasvir monotherapy resulted in an approximately 4 log HCV RNA decline [16] in a phase IIa clinical trial in treatment-naïve HCV genotype 1 patients, Daclatasvir-based triple therapy resulted in extended rapid virologic response (eRVR) in up to 83% of patients, compared to 9% in the control group treated with pegIFN- a and ribavirin only [17].

New DAAs: Selected Clinical Trials in HCV-Monoinfected Patients

Sofosbuvir trials (nucleoside polymerase inhibitor):

- **NEUTRINO trial:** Phase 3 trial of sofosbuvir/pegylated interferon/ribavirin in treatment-naive for 12 weeks in genotype 1, 4, 5, 6; 90% achieved SVR12 [18].
- **FISSION:** Phase 3 trial of sofosbuvir/ribavirin compared to

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sofosbuvir/pegylated IFN/ribavirin in treatment naive for 12 weeks in genotype 2/3 patients; 97% SVR12 in genotype 2 and 56% SVR12 in genotype 3l [19].

- **POSITRON:** Phase 3 trial of sofosbuvir/ribavirin compared to placebo in treatment naive, interferon-ineligible for 12 weeks in genotype 2/3 patients; 93% SVR12 in genotype 2, 61% SVR12 in genotype 3 [20].

- **FUSION:** Phase 3 trial of sofosbuvir/ribavirin in treatment experienced for 12 weeks in genotype 2/3 patients with an 86% SVR12 in genotype 2 and a 30% SVR12 in genotype 3 patients. For 16 weeks, there were a 94% SVR12 in genotype 2 and a 62% SVR12 in genotype 3 [21].

- **VALENCE trial**: Phase 3 trial of sofosbuvir plus ribavirin for genotype 2 or 3; SVR in 93% genotype 2 and 85% genotype 3 [22].

- **ELECTRON:** Phase 2 trial of 12 weeks of sofosbuvir and ledipasvir plus ribavirin for varying durations in genotype 1; SVR12 in 100% of treatment-naive patients, and SVR 12 of 100% in prior null-responders from past treatment-experience [23].

- **LONESTAR**: Phase 2 trial of a fixed-dose combination of sofosbuvir/ledipasvir, with or without ribavirin for varying durations in genotype 1; SVR12 of 100% in treatment-naive patients for 8 weeks of treatment including ribavirin, and SVR4 of 95% in patients failing prior treatment with protease inhibitors' treated for 12 weeks [24].

- **PHOTON-1**: Phase 3 trial of sofosbuvir/ribavirin in genotype 1, 2, 3 patients with HIV/HCV co infection; 76% SVR 12 in genotype 1, 81% SVR-12 in genotype 2, 76% SVR12 in genotype 3 [25].

- **Simeprevir trials (NS3/4a protease inhibitor):**

- **QUEST:** phase 3 trial of simeprevir / pegylated interferon/ ribavirin for 12 weeks followed by 12 weeks of pegylated interferon/ ribavirin alone in genotype 1 treatment naive patients; 86-91% SVR 12 [26].

- **Simeprevir/Sofosbuvir trial:**

- **COSMOS trial:** Phase 2 trial of sofosbuvir plus simeprevir with or without ribavirin for 12 weeks or 24 weeks. In previous null responders with low fibrosis scores, 24 weeks of treatment without ribavirin resulted in 100% SVR12. In patients either treatment naive or prior null responders with high fibrosis scores, 12 weeks of treatment without ribavirin resulted in 100% SVR4 [27].

ABT-450/ritonavir/ABT-333/ABT-267 trials:

AVIATOR: ABT-450/ritonavir plus ABT-333 plus ABT-267 with ribavirin in genotype 1 in treatment naive and prior null responders, 24 weeks of treatment resulted in 93% SVR12 in treatment naive patients, and 24 weeks of treatment resulted in 98% SVR12 in prior null responders [28].

Although above listed trails covers all the treatment aspects in HCV but still clinical challenges remain, including the management of special patient populations for whom data are still limited. These include patients with cirrhosis along with chronic kidney disease, renal failure, and concurrent infection with human immunodeficiency virus, and patients who have undergone solid organ transplantation. Clinical trials are under way to evaluate the treatment options for these patients, who will likely need to wait for the emergence of additional agents before dramatic improvement in sustained virologic response rates may be expected.

One hopes that policymakers and other public health sector stakeholders in Pakistan are paying attention to these developments for the newer oral treatment agents to deal with deadly disease. It is an exciting time for patients and healthcare providers as a new generation of drugs predicting more effective drug treatments are now available. With any luck, in the next decade, medical science should be able to treat and cure more than 90 percent of hepatitis C patients. The greater challenge is identifying patients because most remain undiagnosed and educating medical providers about the new therapies.

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