*Review Article*

# Recent trends in chronic hepatitis C virus treatment

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## Summary

*Hepatitis The hepatitis C virus is the major cause of progressive liver diseases and a public health problem worldwide. At present, hepatitis C has become a curable disease with the use of new interferon-free regimens based on direct-Acting Antiviral agents (DAA.s). Direct-acting antivirals directly target the viral protease, polymerase, or non-structural proteins. These agents have been approved by FDA in various combinations to interrupt HCV replication at different sites. The introduction of DAAs has increased the number of patients who respond to treatment, and has changed radically the treatment of chronic HCV with reported sustained virologic response (SVR) rates exceeding 95% in treating patients. Treatment for chronic HCV is based on guidelines from the Infectious Diseases Society of America (IDSA) and the American Associations for the Study of Liver Diseases (AASLD), in collaboration with the International Antiviral Society-USA (IAS-USA). Based on available resources, patients at high risk for liver-related complications and severe extrahepatic hepatitis C complications should be given high priority for treatment. This article aims to summarize newly available treatment regimens and special considerations for each regimen, such as coinfection with human immunodeficiency virus (HIV), compensated or decompensated cirrhosis, and Post-transplant patients.*

**Keywords:** *Chronic hepatitis C virus; direct-Acting Antiviral agents and sustained virologic response*

## Introduction

Hepatitis C virus (HCV) is a single-stranded RNA virus belonging to the Flaviviridae family. The structure of HCV includes structure proteins (core protein, envelope proteins) and non-structural proteins (NS1, NS2, NS3, NS4B, NS5A and NS5B)[1]. Intracellular virus assembly requires appropriate interaction between core protein and NS5A under a cellular lipid platform[2]. Altered metabolic processes in the infected host are mainly mediated by HCV core protein[3] and NS5A proteins[4]. Egypt has been reported to have the highest population-based prevalence of HCV; nearly 15% in individuals aged 15 to 59 years, and varies by region and age[5]. Nearly half of people aged 50 to 59 years are infected, and modeled incidence rates project more than 500,000 new cases in Egypt each year, stemming from a rate of ~6.9 cases/1000 persons per year[6]. Transmission in Egypt has primarily been attributed to a national anti-schistosomiasis campaign from the 1920s to the 1980s during which 3- to 4-month regimens of parenteral injections were given to children and young adults in parasite-infested areas[7].

## Pathogenesis

The HCV virus has developed a number of strategies to circumvent the immune response of the infected host. These strategies involve mainly three mechanisms, namely the over-riding of induction of interferon, abolishing antiviral effectors induction, and directly interfering with antiviral functions[8]. The most important of these approaches for HCV to

overthrow the host innate immune response is by cleavage of Mitochondrial Anti Viral Signal protein (MAVS) by HCV-encoded NS3/4A protease for a number of reasons. On infection of hepatocytes with hepatitis C virus, one of the major pathways for IFN activation is via RLR signaling, which includes MAVS as a cardinal adaptor protein. In addition, stimulation of IFN transcription is blocked by cleavage of MAVS. Because IFN transcription occurs early in the signaling cascade of innate immunity, this early stage blockade dampens host antiviral response more profoundly than those occurring later in the cascade. Moreover, inactivation of MAVS by proteolysis is more effective than methods utilizing protein-protein interactions. Indeed, this can be seen in infected hepatic cell lines and liver biopsies from patients with hepatitis C more clearly than other forms of escape mechanisms that can only be evidenced by over expression of viral proteins that blocked innate signaling in cells[9].

## Recent trends in treatment.

Introduction of the new interferon-free regimens based on direct-Acting Antiviral agents (DAA's) has revolutionized the field of HCV treatment in Egypt and worldwide. It resulted in marvelous improvement in achieving SVR rates up to 100.0 % in some situations together with reduced adverse events, shortened treatment duration and enhanced effectiveness in difficult to treat groups. DAA of different class (NS5A inhibitors, NS3/4A protease inhibitors, or NS5B polymerase inhibitors) alone or combined with ribavirin also resulted in outstanding improvement in treatment tolerability[10].

### *Genotype 1*

For genotype 1 patients, predominantly prevalent in USA and Europe, many treatment options have been added to the treatment armamentarium. Combination pill that comprise dgrazoprevir (NS3/4Aprotease inhibitor) and elbasvir (NS5A inhibitor) was recommended as the first line treatment. In genotype 1a patients, the treatment duration varies from 12 weeks in patients with NS5A resistant with weighted addition of ribavirin when needed for 16 weeks for those with resistance. For genotype 1b patients, treatment duration is 12 weeks. SVR rates over 95% were achieved regardless of the presence of liver cirrhosis[11]. Another option is the single tablet combination of sofosbuvir (NS5B polymerase inhibitor) and ledipasvir (NS5A inhibitor) administered for a duration of 12 weeks in non-cirrhotic patients to be extended to 24 weeks in treatment-experienced patients with cirrhosis. The reported SVR rates ranged from 93% to 99%[12]. The combination of paritaprevir and dasabuvir is another competitive first line treatment. Utilization typically involves the administration with ribavirin for 12 weeks in non-cirrhotic patients of genotype 1a and without ribavirin in similar patients with genotype 1b. Cirrhotic patients with genotype 1a require administration of the drugs with ribavirin for a period of 24 weeks[13]. Another combination includes sofosbuvir and simeprevir and was used for 12 weeks in genotype 1 patients regardless the cirrhosis status achieving SVR of 92%[14]. In a small number of studies, daclatasvir with sofosbuvir combination offered high SVR rates if more than 90% in non-cirrhotic patients[15]. These results prompted the suggestion that adding weight-based ribavirin to this combination could improve SVR if the duration of treatment was extended to 24 weeks[16].

### *Genotype 2*

Sofosbuvir in combination with ribavirin administered for a period of 12 weeks constitutes the first line of treatment in patients with genotype 2 offering an SVR of 94%[17]. When ribavirin is contraindicated, 12 weeks of daclatasvir and sofosbuvir combination is an alternative[15]. However, in cirrhotic patients, treatment duration may be extended to 16-24 weeks[18].

### *Genotype 3*

Daclatasvir combined with sofosbuvir for 12 weeks is the treatment of choice in most patients with genotype 3infection with SVR rates exceeding 90% in non-cirrhotic patients and the low 58–69% in cirrhotic[19]. However, clinical studies indicate that extending treatment to 24 weeks improved SVR to 80%[16]. Alternatively, 24 weeks regimen combining sofosbuvir and ribavirin can be used with achievable SVR rates exceeding 90% in treatment naïve patients (even those with cirrhosis), but SVR rates diminish considerably in patients who had previously undergone therapy, down to 87% in non-cirrhotic patients and even lower to 62% in cirrhotic patients[20].

### *Genotype 4*

Ledipasvir/sofosbuvir combinations appropriate treatment for genotype 4 patients when administered for 12 weeks affording SVR of 95%[21]. Twelve weeks of paritaprevir, ombitasvir, and Ribavirin combination proposes an effective alternatively with excellent results[22]. Recent FDA approvals in these patients include administration of elbasvir and grazoprevir combination for a period of 12 weeks in treatment-naïve and in combination with weight-based ribavirin for 16 weeks in treatment-experienced patients[22].Additional options include 24 weeks sofosbuvir and ribavirin combination[23]. The recent study of Elsharkawy et al concluded that DAAs are safe and effective in genotype 4 chronic HCV patients. It improves liver necro-inflammatory markers in cirrhotic and non-cirrhotic. Cirrhotic patients require careful observation being more vulnerable for treatment related complications[24].

## Special Patient Populations

### • *HIV/HCV patients*

Patients co-infected with HIV with HCV when treated with telaprevir and boceprevir combination had SVR rates similar to HCV infected patients[25]. One study showed that 12 week treatment regimen with ledipasvir/ sofosbuvir offered SVR of 96%, and even cirrhotic or treatment-experienced patients showed SVR of 94% and 97%, respectively[26]. In another study, co-infected patients treated for either 12 or 24 weeks with combination paritaprevir/ ritonavir, ombitasvir, and dasabuvir accompanied by ribavirin acquired SVR of 92-94% SVR[27]. Co-infected patients with genotype 2-4 showed similar rates of success different DAA combinations[28]. The ALLY-2 study showed that daclatasvir/ sofosbuvir comb-ination in genotypes 1-4provided SVR rate of 96%[15].

### • *African Americans*

Treatment of African-Americans with PEG-IFN and ribavirin was accompanied by relatively high failure rate, a finding that can be accounted for by the presence of a single-nucleotide polymorphism adjacent to the host interleukin-28B (IL-28B) gene as displayed by genome-wide association studies (GWAS)[29,30]. Multiple DAA combinations have shown tremendous improvement in this issue with a rare exception reported by one study when this population showed a SVR of 90% due to unfavorable IL28Bgenotypes[26].

### • *Decompensated HCV cirrhosis*

Administration of sofosbuvir and ribavirin± interferon for 12 weeks was accompanied by 75% improvement in liver function and SVR in 56% of patients[31]. Further studies in patients with decompensated cirrhosis treated for either 12 or 24 weeks with ledipasvir and sofosbuvir and ribavirin demonstrated 85-90% SVR at 12 weeks in genotype 1 patients[32].

### • *Post-transplant patients*

In patients with genotypes 1 and 4, 12 weeks treatment with ledipasvir/sofosbuvir with ribavirin provided SVR of 96% in patients not exhibiting decompensated cirrhosis. Response rates were found to diminish with rise in level of liver decompensation (CTP class B showed 85% SVR while CTP class C had SVR of only 60%)[12]. Twelve weeks, treatment with daclatasvir/sofosbuvir and ribavirin provided a similar SVR of 94% in genotype 1 patients. The same combination can be given to patients with genotypes 2, 3, and 4. If length of treatment requires extending to 24 weeks, either of the above mentioned regimens may be administered minus ribavirin in patients experiencing intolerance[33].

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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