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Review article

Evolution of treatment of chronic hepatitis C virus infection by directly acting anti-viral therapeutics: A glimmer of hope

Abd-Elkhalek, E.[1]*, Kamal, A.[2] & Helmy, A.[3]

[1] *Gastrohepatology Unit, Internal Medicine dept., Specialized Medical Hospital, Mansoura Univ., Egypt*
[2]*Nephrology Unit, Mansoura Urology & Nephrology Center, Mansoura Univ., Egypt.*
[3]*Tropical Medicine & Gastroenterology dept., Assiut Univ. Hospital, Assiut, Egypt.*

* E-mail: ehabdr@yahoo.com

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Abstract:.

HCV was discovered in late 1980s. Few years later the INFα was established as the standard treatment for chronic hepatitis C virus (HCV) infection but with low response rate. This era was followed by consecutive improvements of the INFα based therapy regarding the dosing and pegylationand combined treatment INFα with ribavirin on 1999 which was associated with relative better health related quality of life and favorable clinical outcomes. Recently, the introduction of direct Acting Agents (DAAs) targeting specific viral component revolutionized the treatment of this virus. During the upcoming years, we shall hopefully find a universal and dramatic impact on end-stage liver disease owing to the invention of these oral potent drug protocols against HCV infection.

Keywords:

Hepatitis C virus
Protease inhibitors
Polymerase inhibitors
Sustained viral response
Treatment

Abbreviations: *BOC; boceprevir; CKD; chronic kidney disease. DAAs; direct acting antivirals. DCV; Daclatasvir. HCV GT; hepatitis C virus genotype. HCV; hepatitis C virus. HD; hemodialysis. INF-α; interferon-α. LDV; ledipasvir. OBV/PTV/r; ombitasvir/ paritaprevir/ ritonavir. PI; protease inhibitor. RBV; ribavirin. RNA, ribose nucleic acid. SIM; simeprivir. SOF; sofosbuvir. SVR; sustained virological response. TLV; telaprevir WHO; world health organization.*

Conflict of Interest & Disclosures: None

1. Introduction

According to the World Health Organization (WHO), nearly 130-170 million people are infected with hepatitis C virus (HCV all over the world, corresponding to about 2.5 % of the world's total population. There are notable regional differences. In some countries, e.g., Egypt, the prevalence is >10 %. In Africa and the western Pacific the prevalence is significantly higher than in North America and Europe, with >350000 people die each year secondary to HCV-related complications [1-3]. The combination of pegylated interferon-α (Peg-IFN-α) and ribavirin (RBV) was recommended as the standard of care (SOC) therapy for chronic hepatitis C for nearly about a decade. In 2011, tissue culture studies led to the discovery of directly acting antivirals (DAAs) against HCV, namely the NS3/4A protease inhibitors (telaprevir; TLV and boceprevir; BOC), which got approval to treat HCV-genotype-1 (HCV GT1) infection, each in a triple combination with Peg-IFN-α and RBV. These treatments allowed higher rates of sustained virological response (SVR) than the SOC regimen, but with low tolerability and high cost leading to reduced adherence and/or early discontinuation of therapy. This has been overcome with the second and third generations of DAAs introduced over the last 3 years, and gave a glimmer of hope to all concerned with chronic HCV infection. This review focuses on the use of the markers of HCV infection and replication, of laboratory and instrumental data to define the stage of the disease and of predictors, if any, of response to therapy in the DAA era. The article new DAAs and is addressed particularly to physicians who take care of patients with chronic HCV in their everyday practice.

2. Genomic Structure of HCV

The genome of the hepatitis C virus consists of one 9.6 kb single-stranded RNA molecule with positive polarity. The genomic organization of the HCV-RNA serves as messenger RNA (mRNA) for the translation of viral proteins. The linear molecule contains a single open reading frame (ORF), which codes for a precursor polyprotein of about 3000 amino acid residues. During viral replication the polyprotein is cleaved by host and viral enzymes into three structural proteins (core, E1, E2) and seven nonstructural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, NS5B, fig. (1) [4-7].

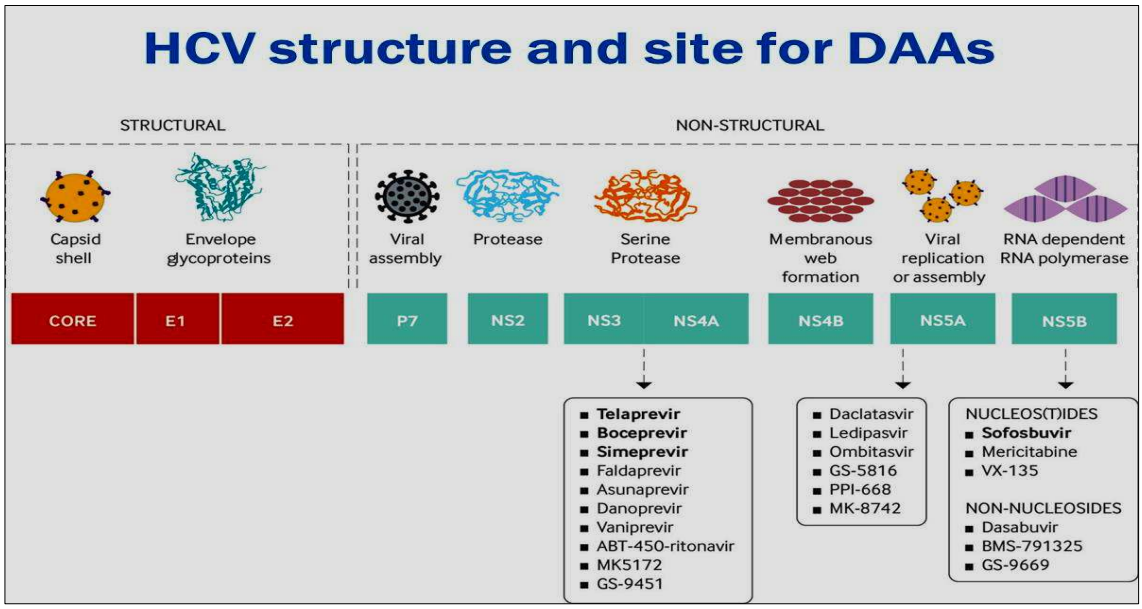

Figure (1) Structure of the hepatitis C virus genome and the directly acting antivirals with their site of action.

3. Treatment of Chronic HCV Infection

3.1. *Goal of therapy*

In most of countries, HCV prevalence has already peaked, and is starting to decline due to two main issues: the implementation of blood screening programs and the treatment updates. The aim of antiviral therapy is to eradicate HCV through elimination of the virus. This is achieved when HCV-RNA remains negative three months after the end of treatment (sustained virological response, SVR). The American FDA has accepted HCV-RNA negativity 12 weeks after the end of treatment as an endpoint because HCV relapse usually occurs within the first 12 weeks after the end of treatment. For new treatment regimens with the direct antiviral agents (DAAs), even HCV-RNA negativity 4 weeks after end of treatment has been shown to be highly predictive for achieving long-term viral clearance (*positive predictive value* >99 %) [8].

3.2. *Development of anti-HCV treatment*

Before recognition of HCV as the infectious agent for non-A, non-B hepatitis, interferon α (IFNα) led to an adjustment of transaminases and an improvement of liver histopathology in most patients [9,10]. After the recognition of HCV, it became possible to achieve a progress of treatment as the persistent disappearance of HCV-RNA from serum. Since then, SVR rates have

increased from 5-20 % with IFN monotherapy up to 40-50 % with the use of a combination of pegylated IFNα and ribavirin (RBV) [11]. Different HCV genotypes (HCV GTs) show different SVR rates to therapy [12]. The development of DAAs against HCV has revolutionized the treatment of chronic hepatitis C. The main targets for DAAs are the NS3/4A protease, NS5B polymerase and the NS5A replication complex. Antivirals acting at the these 3 targets differ in their resistance barrier, genotypic coverage and antiviral potency or efficacy, fig. (2). The ideal combinations of different DAAs from these different classes should allow very potent treatments with broad genotypic barrier, and highest resistance barrier. In 2011, the first selective protease inhibitors (PI) were approved for patients with HCV GT1.In 2014, new DAAs were approved. Simeprevir (SMV) (SIM) (Olysio^{R}) was the first once-daily PI. Sofosbuvir (SOF) (Sovaldi^{R}) is the first available once-daily NS5B polymerase inhibitor (approved 12/2013 by FDA).

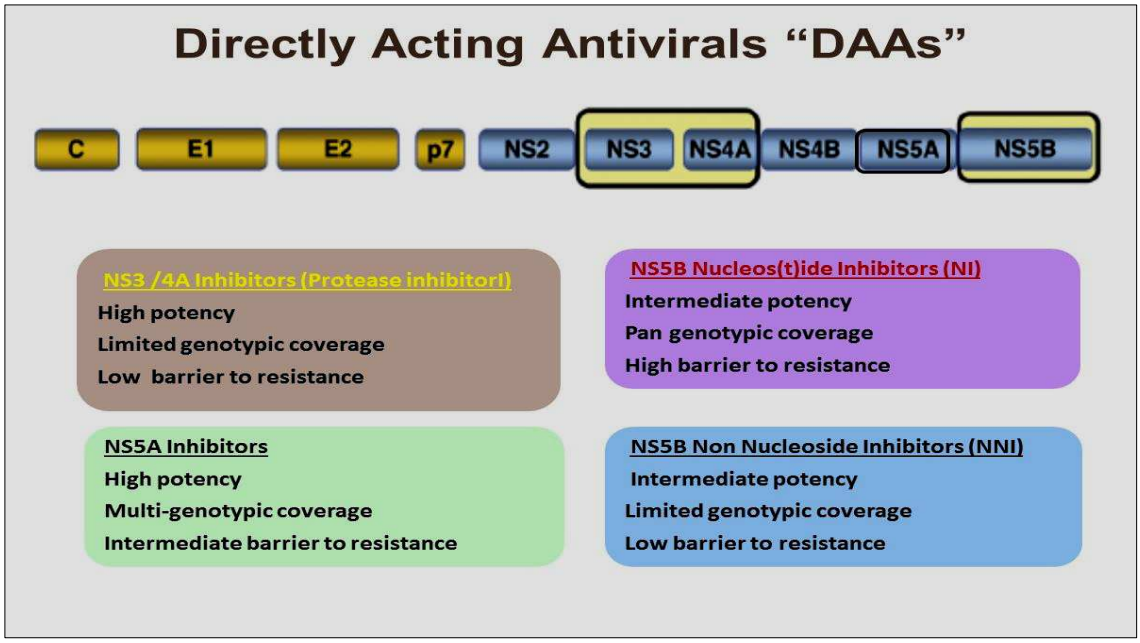

Figure (2) Grouping of directly acting antivirals (DAAs) according to their resistance barrier, genotypic coverage and antiviral potency or efficacy.

3.3. *Newer anti-HCV drugs*

In the last few years, numerous DAAs have been implemented successfully in treatment algorithms of HCV infection, tab. (1). As combination therapy with pegylated INFα (PEG-IFNα), ribavirin, and/or other DAAs, potent DAA-based regimens result in HCV eradication in the vast majority of patients with chronic hepatitis C [13]. Most DAAs were then approved over the

last 3 years [14-24]. In principle, each of the four HCV structural and six non-structural proteins, HCV-specific RNA structures such as the IRES, as well as host factors on which HCV depends, are suitable targets for DAA agents.

Table (1) Relevant direct acting anti-viral (DAA) treatment regimens

Drug name	Mechanism of action	Dose/day mg.	Reference
Boceprevir (BOC)	NS3/4A protease inhibitors	800	14, 15
Telaprevir (TLV)	NS3/4A protease inhibitors	2250	16
Simeprevir (SMV)	NS3/4A protease inhibitors	150	17
Sofosbuvir (SOF)	Nucleoside analog NS5B polymerase inhibitors (NI)	400	18, 19, 25, 26
Daclatasvir (DCV)	NS5A inhibitor	60	20-22
Ledipasvir (LDV)*	NS5A inhibitor	90	23, 24
VIEKIRAX® Qurevo (Ombitasvir / Paritaprevir / Ritonavir)	NS3/4A protease inhibitors, Non-nucleoside analog NS5B polymerase inhibitors (NNI), and NS5A inhibitor	25 150 100	28, 29
Velpatasvir	NS5A inhibitor	25 or 100	31

** The combination of ledipasvir (LDV) and sofosbuvir (SOF) is available as a single tablet fixed-dose combination (Harvoni®, Gilead Sciences). The tablet contains the NS5B polymerase inhibitor SOF (400 mg) and the NS5A inhibitor ledipasvir (LDV, 90 mg).*

3.4. *Treatment of HCV genotypes 4, 5, and 6*

Treatment concepts for GT1 are generally valid for GT4-6. Most of the new DAAs are also effective against GT4-6. Thus, dual therapy with PEG-IFN and RBV can be avoided if possible. Triple therapy of SOF + PEG-IFN/RBV for 12 weeks has resulted in 96-100 % SVR in GT4-6 patients [25]. However, the number of patients was low (n=35) but the data was sufficient for the approval of SOF for all genotypes. SOF/RBV for 12-24 weeks was investigated in 60 patients with genotype 4, tab. (2). SOF/RBV for 24 weeks showed the best results with 100 % SVR for naïve and 87 % for treatment experienced patients [26]. SOF/RBV is available in Egypt for 1% of the regular price (ie, 600 €). Also SOF/LDV is approved for GT4 although data are limited. SOF/LDV given for 12 weeks resulted in 95 % SVR in 21 GT4 patients [27]. The ombitasvir/ paritaprevir/ ritonavir (OBV/PTV/r) are also effective against GT1 and GT4 [28,29]. The PEARL-I study recruited 135 GT4 patients. Naïve patients received either OBV/PTV/r or OBV/PTV/r with RBV for 12 weeks. A

third group of treatment-experienced patients were also treated with OBV/PTV/r with RBV for 12 weeks. Naïve patients achieved 91 % SVR without RBV and 100 % SVR with RBV. All treatment-experienced patients were cured as well, tab. (2). Unfortunately, patients with cirrhosis were not included. Thus, OBV/PTV/r with RBV for 12 weeks is recommended for both GT1 and GT4 infected-patients without cirrhosis. Patients with cirrhosis should be treated for 24 weeks, but sufficient data are lacking. Data with IFN free regimens are rare for GT5 and 6. SOF/LDV for 12 weeks has been studied in 25 naïve GT6 patients. Most patients were treatment-naïve and showed SVR of 96 % [30].

Table (2) Sustained viralogical response rates of DAAs treatment in HCV genotype 4-6 infection*

Study	Treatment	SVR
RESTORE [30] **n=107 GT4** **n=72 exp'd**	180 µg PEG-IFN α-2a, 1000-1200 mg RBV 24-48weeks + 150 mg SMV 12 weeks	65 % Naïve: 83 % REL: 91 % PR: 60 % NULR: 40 %
NEUTRINO [25] **n=35 GT4-6**	180 µg PEG-IFN α-2a, 1000-1200 mg RBV + 400mg SOF 12Weeks	96 % GT4 (n=28) 100 % GT5 (n=1) 100 % GT6 (n=6)
Ruane [26] **n=60 GT4**	a) 400 mg SOF + 1000-1200 mg RBV 12 weeks b) 400 mg SOF + 1000-1200 mg RBV 24 weeks	68 %; Naïve: 79%&Exp.: 59 % 93 % Naïve: 100 % Exp.: 87 %
Kohli [27] **n=21 GT4**	400/90 mg SOF/LDV 12 weeks	95 %
PEARL-I [29] **n=135 GT4**	a) 25 mg/150/100 mg OBV/PTV/r + 1000-1200mg RBV 12 weeks b) 25 mg/150/100 mg OBV/PTV/r 12 weeks c) 25 mg/150/100 mg OBV/PTV/r + 1000-1200mg RBV 12 weeks	Naïve: 100 % Naïve: 91 % Exp: 100 %
Feld [31] **n=624 GT 1-6** **32 % exp'd** **19 % cirrhotics**	400 mg SOF / 100 mg velpatasvir	99 %
Gane [32] **n=25 GT6** **92 % naïve**	400/90 mg SOF/LDV 12 weeks	96 %

** Studies are not head-to-head and SVR between studies are difficult to compare because they had significant differences in genetic and socioeconomic backgrounds. RBV: ribavirin, SOF: sofosbuvir, LDV: ledipasvir, PTV/r: paritaprevir/ritonavir, OBV: ombitasvir, Exp.: treatment experienced patients.*

3.5. *New hope for specific groups*

More recognition of sub genomic and genomic replication systems of different virus genotypes lead to major advances in the virus molecular

virology. These advances paved the way for construction of multiple therapeutic agents targeting viral specific small molecules with potent antiviral effect and fitting some specific risk groups providing a promising hope for getting successfully treated. Specific risk groups for HCV infection include patients with chronic kidney disease (CKD) mainly those maintained on chronic hemodialysis (HD) reaching prevalence of 80 % [2]. Chronic HCV patient on HD are at increased risk for morbidity and mortality in pre and post kidney transplantation in from of increased acute rejection episodes, HCV-induced glomerular disease, infections, new onset diabetes after transplantation, cancer and rapid progression of liver fibrosis [32]. A prospective study in our center confirmed worst graft and patient outcomes in HCV positive Egyptian renal transplant patients [33]. Kidney transplant recipients with chronic HCV infection are considered a hard to treat group. Immunosuppressive medication used post transplantation facilitates the viral infection and replication making the infection harder to eradicate. On the other hand, INFα based protocols carry a high risk for graft dysfunction (51%) and a low rate of SVR (17-38%) [34]. New discovered DAAs have been approved for the treatment of genotype 4, but the data about the efficacy and safety of using these agents post-renal transplantation are sparse [35]. Relative to their time of usage, there are positive data supporting the combination of nucleotide analogue NS5B polymerase inhibitor (SOF 400 mg./day) and HCV protease inhibitor (Semiprevir 150 mg/day) that blocks viral maturation, for 12 weeks in treatment of chronic HCV genotype 4 infection (AASLD-IDSA guidelines, June, 2015) [36, 37].

4. Conclusion

Indeed, the discovery of DDAs has revolutionized the treatment of chronic HCV infection. Many drugs and different combinations are currently existing and passed phase 3 trials. The choice of the ideal combination is far from being reached at the moment. This is of concern in patients with existing cirrhosis especially those with Child Grade B or C, those with chronic kidney disease, those with previous anti-HCV therapy, and also in children as well as those with co-infection with hepatitis B virus or HIV. Data regarding resistance typing and the predictors of response are evolving and more are still needed. The upcoming decade or even earlier, carries good news and a bigger hope for patients with chronic HCV.

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