Mini-Review

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Research progress on the direct antiviral drugs for hepatitis C virus

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Summary **Hepatitis C, caused by the hepatitis C virus (HCV) that attacks the liver and leads to inflammation, is a severe threat to human health. Pegylated interferon α (INF-α) and ribavirin based therapy was once the standard therapy for HCV infection. However, it is suboptimal in efficacy and poorly tolerated in some patients. In the last five years, four classes of direct antiviral drugs (NAAs) that target non-structural proteins (NS) of the virus including NS3/NS4A, NS5A, and NS5B have been developed and opened a new era in HCV treatment as they are more effective and tolerable than the INF-α and ribavirin combination regimen. Importantly, the newly introduced multiple NAAs combination therapy makes it possible to eradicate all genotypes of HCV. We review recent progress on the research and development of DAAs in the present article.**

Keywords: HCV, interferon, ribavirin, NAA, NS3/NS4A, NS5A, NS5B

1. Introduction

Hepatitis C virus infection (HCV), which occurs most commonly in Africa and Central and East Asia, is a significant public health problem with approximately 130-200 million people around the world infected at present (*1-4*). Acute HCV infection is rarely associated with life-threatening disease and about 15-45% of infected persons spontaneously clear the virus within 6 months of infection without any treatment (*5*). The remaining 55-85% of persons will develop chronic HCV infection, which is recognized as one of the major causes of chronic liver diseases such as liver cirrhosis and hepatocellular carcinoma (HCC) (*5-7*). Specifically, the risk of liver cirrhosis is between 15-30% within 20 years in people with chronic infection (*5*). According to the data disclosed by World Health Organization (WHO), approximately 700,000 people die each year from hepatitis C-related liver diseases (*5*).

The goal of hepatitis C treatment is to obtain sustained virological response at 12 weeks (SVR12) which is recognized as the measure of treatment success and defined as undetectable HCV RNA in the blood at the end of treatment and again 12 weeks following treatment end (*8,9*). Multiple evidences support that antivirus treatment helps improve hepatic histology, prevents or delays the occurrence of liver cirrhosis, and decreases the incidence of HCC (*9,10*). Interferon α (IFN-α) with established clinical efficacy has long been used for treatment of HCV infection. Combination of pegylated IFN-α and ribavirin, a nucleoside analogue, was once the standard therapy, which cured approximately half of treated patients, but caused frequent and sometimes life-threatening adverse reactions (*11*). In the recent five years, new antiviral drugs, called direct antiviral agents (DAAs), have been developed and revolutionized the treatment of HCV because they are much more effective, safer and better-tolerated than the older therapies (*8*). The progress of DAAs research and development is reviewed in the present article.

2. Gene structure and genotypes of HCV

HCV, a positive-sense single-stranded RNA virus of the family Flaviviridae, consists of a core of genetic material (RNA), surrounded by an icosahedral protective shell of protein, and is further encased in a lipid (fatty) envelope of cellular origin (*12*). The genome of HCV consists of a single open reading frame that is translated to produce a single protein product. This single product is then proteolytically processed by viral and cellular proteases into 10 smaller proteins which are grouped

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into structural proteins including Core protein, envelope glycoproteins E1 and E2, and p7 and non-structural proteins (NS) including NS2, NS3, NS4A, NS4B, NS5A, and NS5B (*13*). The structural proteins form the skeletal structure of the virus particle while non-structural proteins act as enzymes or regulatory factors that play critical roles in virus replication. Among the non-structural proteins, NS3 functions as a serine protease and forms a heterodimeric complex with NS4A that acts as a cofactor of the proteinase (*13*). NS5A is a hydrophilic phosphoprotein which plays an important role in viral replication, modulation of cell signaling pathways, and the interferon response (*14*). The NS5B protein is the viral RNA dependent RNA polymerase, which catalyzes the polymerization of ribonucleoside triphosphates (rNTP) during RNA replication (*15-17*). Given the critical role of NS3/NS4A, NS5A, and NS5B in the viral life cycle, they are currently focused on as major targets in development of DAAs.

A naturally high rate of genetic mutation due to low fidelity of RNA replication generates genetic diversity of HCV (*18*). Based on genetic differences between HCV isolates, the HCV species is classified into six genotypes (1-6) with several subtypes within each genotype. Genotype 1, which includes subtype 1a and 1b seen in almost all cases (31% and 68%, respectively), constitutes 40-50% of all HCV infections and is the most prevalent genotype worldwide (*19*). The next most prevalent genotype is genotype 3 (about 30%), followed by genotypes 2 and 4 (about 10% each), genotype 6 (about 5%), and genotype 5 (less than 1%) (*19*). Mixed genotype infections are also seen in a small proportion of patients (*19*). Among all subtypes of HCV, subtypes 1a, 1b, 2a, and 3a are globally distributed and are considered "epidemic subtypes" (*8*). Genotype is clinically important in determining potential response to medications. For example, genotypes 1 and 4 are less responsive to IFN-α-based treatment than are the other genotypes (2 , 3, 5, and 6) (*20*), which leads to difficulties in clearing HCV of these two genotypes. On the other hand, the latest developed DAAs combination regimens have the potential to eradicate all genotypes of HCV, hence enlarging the patient population who may benefit.

3. Direct antiviral drugs for HCV

Thus far, four classes of DAAs have been developed based on three targets. They are protease inhibitors targeting NS3/NS4, nucleotide analogues and non-nucleosides targeting NS5B, and NS5A phosphoprotein inhibitors (Table 1). Because the antivirus efficacy of individual DAAs usually depends on HCV genotype, genotypic subtype and disease severity (*e.g.*, cirrhosis) and many DAAs are prone to induce HCV resistance when used alone, combination regimens including two, three or even four DAAs, without pegylated IFN-α, have been developed and have become the new standard of care for HCV.

3.1. *Sofosbuvir and combination therapies*

Sofosbuvir, a nucleotide analogue targeting NS5B, was firstly approved by the US Food and Drug Administration (FDA) in 2013 for treatment of HCV genotypes 2 and 3 in combination with ribavirin or treatment-naive patients with HCV genotypes 1 and 4 in combination with ribavirin and pegylate IFN-α (*21*). Sofosbuvir is now used as the backbone for several interferon-free regimens. The combination of sofosbuvir with the NS5A inhibitor ledipasvir as a fixed-dose, once-daily, single-tablet regimen was approved by FDA in 2014. It approaches but does not achieve pan-genotypic status, with efficacy demonstrated against HCV genotype 1, 4, 5, and 6 infections (*8*). Evidence is lacking for this regimen in genotype 2, and it has only limited activity against genotype 3 without the addition of ribavirin (*8*). Given this reason, sofosbuvir plus ledipasvir is not recommended for use in genotypes 2 and 3. On the other hand, the combination of sofosbuvir with another NS5A inhibitor velpatasvir as a once-daily, single-tablet, pangenotypic regimen was recently approved for the treatment of adults with chronic HCV genotypes 1-6 in the USA, EU and Canada (*22*). In the phase III ASTRAL trials, once-daily oral sofosbuvir plus velpatasvir for 12 weeks provided high rates of SVR12 in treatment-naive and -experienced patients with chronic HCV genotype 1-6 infection (*22*). This

Table 1. The direct antiviral drugs (DAAs) developed for hepatitis C virus (HCV)

DAAs (target)	Combined agents (target)	HCV genotype	Status	*Ref.*
Sofosbuvir (NS5B)	Ribavirin	1, 4	Approved	*21*
	Ribavirin and IFN-α	2, 3	Approved	*21*
	Ledipasvir (NS5A)	1, 4, 5, 6	Approved	*8*
	Velpatasvir (NS5A)	1, 2, 3, 4, 5, 6	Approved	*22*
	Velpatasvir (NS5A) + Voxilaprevir (NS3/4A)	1, 2, 3, 4, 5, 6	Phase III	*27*
Daclatasvir (NS5A)	IFN-α + Ribavirin	1, 3, 4	Approved	*28*
	Asunaprevir (NS3/4A)	1	Approved	*30*
	Sofosbuvir (NS5B)	1, 2, 3, 4	Approved	*32*
Simeprevir (NS3/4A)	IFN-α + Ribavirin	1, 4	Approved	*34*
	Sofosbuvir (NS5B)	1	Approved	*38*
	Samatasvir (NS5A)	1, 4	Phase II	*39*
Dasabuvir (NS5B)	Ombitasvir (NS5A) + Paritaprevir (NS3/4A) + Ritonavir (P450 3A4)	1	Approved	*40*

regimen represents a valuable treatment option in adults with chronic HCV genotype 1-6 infection.

The combination of sofosbuvir, velpatasvir, and voxilaprevir, an investigational NS3/4A protease inhibitor, as a fixed-dose, once-daily regimen (SOF/VEL/VOX) is currently being evaluated for its efficacy and safety in treatment of genotypes 1-6 chronic HCV infection. Thus far, four phase 3 clinical studies including POLARIS-1, POLARIS-2, POLARIS-3, and POLARIS-4 on this regimen have been conducted. The POLARIS-1 and POLARIS-4 studies aimed to evaluate the combination regimen in patients who experienced previous NAAs treatment. The POLARIS-1 study enrolled patients who failed prior treatment with an NS5A inhibitor (*23*). The POLARIS-4 study enrolled patients who failed prior treatment with a DAA that was not an NS5A inhibitor, most with either an NS5B inhibitor alone (73%) or an NS5B inhibitor and an NS3/4A protease inhibitor (25%) (*24*). The POLARIS-2 and POLARIS-3 studies were designed to evaluate the SOF/VEL/VOX regimen in patients without previous NAAs treatment. The POLARIS-2 study enrolled patients with genotype 1-6 HCV infection with or without compensated cirrhosis (*25*), while the POLARIS-3 study enrolled patients with genotype 3 HCV infection, all of whom had compensated cirrhosis (*26*). In October 2016, results of these clinical studies were announced by the sponsor company Gilead (*27*). According to their report, the POLARIS-1, POLARIS-3, and POLARIS-4 studies met their respective pre-specified primary endpoints for patients receiving SOF/VEL/VOX. The POLARIS-2 study did not meet its primary endpoint; with a pre-specified 5% margin, the SVR12 rate for patients receiving treatment with SOF/VEL/VOX for eight weeks was not statistically non-inferior to the SVR12 rate for patients receiving SOF/VEL for 12 weeks. Results of these studies suggest that combining three potent antivirals with different mechanisms of action provided high cure rates for patients who have failed other highly effective oral DAA regimens.

3.2. *Daclatasvir and combination therapies*

Daclatasvir, an inhibitor of NS5A, was approved for treatment of HCV genotypes 1, 3, and 4 only in combination with interferons and ribavirin and also with some other DAAs such as asunaprevir, beclubavir, and sofosbuvir to overcome drug resistance, increase antiviral efficacy and decrease side effects (*28*). Asunaprevir, which is a NS3/4A inhibitor, has shown high treatment efficacy when used in combination with daclatasvir in patients with HCV genotype 1 (*29, 30*). Currently, the combination of the asunaprevir and daclatasvir regimen has been mainly used in patients with HCV genotype 1 infection in Japan. Subtype 1a has less been evaluated, and it seems that this regimen is appropriate only for HCV subtype 1b (*31*). The addition of beclubavir, an inhibitor of NS5B, to the daclatasvir/asunaprevir regimen was found to improve the SVR rate in HCV-infected patients (*31*). This regimen has been mainly used for the treatment of patients infected with HCV genotype 1 (subtypes 1a and 1b) and 4. The daclatasvir and sofosbuvir combination regimen was approved by the European medicine agency for treatment of genotype 1-4 infections in 2014, followed by the FDA for treatment of genotypes 1 and 3 (*32*). According to several meta-analyses that analyzed the efficacy of this regimen on different genotypes, daclatasvir/sofosbuvir with and without ribavirin can be considered as a highly useful treatment option in treatment-naïve or treatment-experienced patients with genotype 1 and 3 infections with and without cirrhosis (*31,33*). The ability of daclatasvir to combine with other DAAs for treatment of patients with HCV infections under different conditions makes it a good choice for HCV treatment.

3.3. *Simeprevir and combination therapies*

Simeprevir is a NS3/4A inhibitor that was approved in recent years for treatment of chronic HCV genotype 1 or genotype 4 infection in treatment-naive or previously treated adults, including those with HIV coinfection, in combination with pegylated IFN-α and ribavirin and with other NAAs such as sofosbuvir (*34-37*). It is not recommended in patients in whom prior treatment with a regimen that included simeprevir or any other HCV protease inhibitor failed and in patients with moderate or severe hepatic impairment (Child-Pugh class B or C) (*34*). Screening for presence of NS3 Q80K polymorphism is strongly recommended prior to initiation of the regimen consisting of simeprevir, pegylated IFN-α, and ribavirin (*34*). An alternative therapy may be considered in patients infected with HCV genotype 1a containing Q80K polymorphism (*34*). The regimen containing simeprevir and sofosbuvir is used in treatment-naive or previously interferon-treated patients with HCV genotype 1, with or without cirrhosis (*38*). Duration of this regimen is 24 weeks and 12 weeks, respectively, for patients with or without cirrhosis (*38*). Screening of NS3 Q80K polymorphism may also be instructive prior to initiation of simeprevir in conjunction with sofosbuvir (*34*). Combination of simeprevir and samatasvir, an investigational NS5A inhibitor, is currently undergoing phase 2 clinical trials for evaluation of its efficacy in treatment of chronic HCV infection (*39*).

3.4. *Ombitasvir/paritaprevir/ritonavir plus dasabuvir*

The regimen containing a fixed-dose combination of ombitasvir, paritaprevir, and ritonavir and dasabuvir (marketed as Viekira Pak™) was approved by FDA

and other regulatory agencies for the treatment of genotype 1 chronic HCV infection, including those with compensated cirrhosis (*40*). This regimen, also called the "3D" regimen, consists of three DAAs targeting different non-structural proteins, *i.e.* ombitasvir inhibiting NS5A, paritaprevir inhibiting NS3/NS4A, and dasabuvir, a non-nucleoside inhibiting NS5B. The regimen also consists of a cytochrome P450 3A4 inhibitor ritonavir, which can increase the plasma concentration of paritaprevir (*41*). Based on the results of the clinical trials, this regimen is suitable for treating patients infected with hepatitis C genotype 1b (*42,43*). It may be possible to use this combination to treat patients infected with genotype 1a if they have not previously been treated and do not have cirrhosis, but the addition of ribavirin is needed to maximize the response (*42*). While the five-drug regimen is very effective, it will require careful selection of patients and checking product information to avoid drugs that either interact or are contraindicated (*44*). As three new drugs are involved in this regimen, it should be cautioned that unforeseen problems may emerge in the future.

4. Conclusion

Chronic hepatitis C has been a great healthcare concern because of its high prevalence worldwide. Treatment with pegylated IFN-α and ribavirin was once the standard therapy, but poor tolerability and suboptimal response rates increased the likelihood of therapeutic failure. Introduction of DAAs opened a new era in HCV treatment with the possibility of interferon-free therapy, SVR rates approaching 100%, reduced duration of therapy, and improved tolerability. In this aspect, DAAs of the same or different classes have been introduced one after another in close succession in the last five years. Each class of DAAs targets a specific viral protein such as NS3/4A, NS5A and NS5B. The combination of DAAs with different mechanisms reduces the risk of occurrence of HCV resistance and enlarges the patient population who may benefit. Nevertheless, many unknowns still remain with the new drugs combination therapy such as potential drug-drug interactions, which warrant further in-depth studies in the future.

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