Hepatitis: A Global Health Concern

Chapter 4

The Development of Anti-Hepatitis C Virus in the Late Epoch of Direct-Acting Antiviral Agents

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Abstract

About 130-170 million people, is estimated to be infected with the hepatitis C virus (HCV). Chronic HCV infection is one of the leading causes of liver-related death and in many countries it is the primary reason for having a liver transplant. In 2011 approval was given for the first direct acting antiviral agents (DAA), boceprevir and telaprevir, for treatment of genotype 1, in combination with traditional dual therapy. This strategy managed to increase the rates of sustained viral response (SVR) in both naive patients and in retreated patients, but with greater toxicity, interactions and cost, as well as being less safe in patients with advanced disease, in whom this treatment can trigger decompensation or even death. The recent, accelerated incorporation since 2013 of new more effective DAA, with pan-genomic properties and excellent tolerance, besides increasing the rates of SVR (even up to 100%), has also created a new scenario: shorter therapies, less toxicity and regimens free of PEG/RBV. This has enabled their almost generalised applicability in all patients. With the widespread use of DAAs and the update of guidelines, anti-HCV treatment has entered an era of oral drug therapy, in other words, the DAA era. However, it should be noted that most of the scientific evidence available is based on expert opinion, case-control series, cohort studies and

phase 2 and 3 trials, some with a reduced number of patients and select groups.There are many problems in the use of DAAs for treatment of HCV.

Keywords: Hepatitis C virus; Chronic hepatitis C; Hepatocellular carcinoma; Direct-acting antiviral agents

1. Introduction

Chronic hepatitis C (CHC), the global health issues, could cause liver cirrhosis, hepatocellular carcinoma (HCC) and other serious diseases associated with the liver, which could lead to death. The treatment of hepatitis C virus (HCV) is therefore the subject extensively concerned by the whole society. The development ofanti-HCVtherapy could be divided into threephases. In 2011, it was the PR scheme: peginterferon plus ribavirin (ribavirin, RBV). From 2011 to 2015, it was thehybrid age, besides the PR scheme, there were also direct-acting antiviralagents (DAAs) and DAA. Then in 2016, the European Association for the Study ofthe Liver (EASL) has completely entered the DAA age, and the PR scheme was no longer recommended. The United States Food and Drug Administration (FDA) has approved the following, currently commercialised DAA: Sofosbuvir (Sovaldi) [1], Simeprevir (Olysio) [2], Daclatasvir (Daklinza) [3], Sofosbuvir + ledipasvir (Harvoni) [4], Ombitasvir-Paritaprevir/Ritonavir and dasabuvir (Viekirax) [5]. In the meantime, drugs pending commercialization in the near future are combinatsions of various antivirals. MSD (Merck Sharp and Dohme) combo: Grazoprevir (MK-5172), 100 mg, a second generation protease inhibitor, + Elbasvir (MK-8742), 50 mg, a second generation NS5A inhibitor [6]. BMS (Bristol-Myers Squibb) combo: Asunaprevir+ daclatasvir+beclabuvir: A combination of daclatasvir, asunaprevir (NS3 protease inhibitor), and beclabuvir (a non-nucleoside NS5B polymerase inhibitor) with activity in genotypes 1, 2, 3, 4 and 5; and variable activity in genotype 6 [6,7]. The main inconvenience of these new drugs is their high cost. This necessitates selection and prioritization of candidate patients to receive them, via strategies established by the various national organizations, in accordance with the recommendations of scientific societies. With the DAAs appearing on the market, the anti-HCV therapy has gone into the late DAA epoch. In this epoch, how to develop workable, practical as well as economical anti-HCV therapy based on different patients individual need has become more complicated and challengeable. The purpose of this article is to review the drugs currently available for the treatment of HCV.

2. DAA Came Out

DAAs do really have lots of advantages such as the high efficiency, conveniences, less adverse drug reaction, short course and high curing rate [8]. Especially, the DAAs could provide another option for the patients who cannot tolerate the PR therapy and other special crowd. The anti-HCVDAAs update rapidly and could be checked on the website (http://www.hcvadvocate.org/hepatitis/hepC/HCVDrugs.html). The first DAA medicine Boceprevir (BOC) came out in 2011, followed with the second drug Telaprevir (TVR). Both of the two drugs were terminated in 2015. In the same year, the third drug Asunaprevir (ASV) came out in

Japan. All these three drugs were the first generation protease inhibitors (PI) of NS3/4A that aimed at 1/4 genotype (GT) HCV patients. Simeprevir (SMV) which came out in 2013 belong to the second generation of NS3/4A. In the same year, towards HCV NS5B, Gileads listed Sofosbuvir (SOF), the nucleotide analog of Polymerase inhibitor, which could applied to all the treatment of GT. In 2015, one kind of single drug towards NS5A protein inhibitor came out for the treatment of GT 3. As a matter of fact, anti-HCV therapy has gone into the late DAA epoch after the appearance of DCV. The DAA target drugs which aimed at HCV replication have been already on the market for their accessibility. The anti-HCV DAA then could make improvement based on the existing drugs. And 3 known targets could combine in different patterns, NS3/4A, NS5A and NS5B [9]. The order of the single drugs appearing on the market was NS3/4A(PI), then NS5B, then NS5A. NS3/4A and NS5B have relatively clear protein functions and enzymatic activity, which makes it easier to develop inhibitor. For NS3/4A, the antiviral activity of the single drugs would be ABT-493>Grazoprevir>Vedroprevir>ASV. As for NS5A, it would be ABT-530>Velpatasvir(VEL)>Ravidasvir>Elbasvir(ELB). However, the chance for them to come outon the market with great breakthrough is quite slim.

3. Present Status and Future Development Fixeddosage Combination (FDC)

Nowadays, the fixed dosage combination (FDC) came out on the market in the following sequence: (1)Harvoni: SOF+LDV(400/90 mg), GT 1/4/5/6,2014-10-10; (2) Virekira Pak:

OBV+PTV+R+DSV(12.5/75/50/250mg), GT1/4,2014-12-19; (3) Technivie:OBV+PTV+R(12.5/75/50/250 mg) GT 4, 2015-07-24; (4) M2: GZV+ELB (100/50mg), GT 1/4, 2016-01-28; (5) Epclusa: SOF+VEL (400/100 mg). Because of the poor treatment within the anti-HCV single drugs and their quick resistance development, we employed a similar treatment as human immunodeficiency virus (HIV), the cocktail therapy. Up to now, there are four major categories of drugs towards three targets used for anti-HCV treatment : NS3/4A , NS5A, NS5B (nucleoside) and NS5B (nonnucleosides), which could combine others in eleven modes. Those would be (1) NS3/4A+NS5A+NS5B (nucleoside + nonnucleosides); (2) NS3/4A+NS5A+NS5B (nonnucleosides); (3)NS3/4A+NS5A+NS5B (nucleoside); (4)NS3/4A+NS5B (nucleoside + nonnucleosides); (5) NS3/4A+NS5B (nucleoside); (6) NS3/4A+NS5B (nonnucleosides); (7) NS5A+NS5B (nucleoside + nonnucleosides); (8)NS5A+NS5B (nucleoside); (9)NS5A+NS5B (nonnucleosides); (10)NS3/4A+NS5A; (11)NS5B (nucleoside)+NS5B (nonnucleosides) .

We could find that the NS5B were all nucleoside analogues when combining with the other two targets NS3/4A and NS5A. That may be due to the better effects of the nucleoside analogues towards NS5B inhibitor than that of the nonnucleosides analogues. Theoretically, there may be 8 combinations:

(1) NS3/4A+NS5A+NS5B (nucleoside + nonnucleosides);

(2)NS3/4A+NS5A+NS5B (nonnucleosides);

(3) NS3/4A+NS5A+NS5B (nucleoside);

(4)NS3/4A+NS5B (nucleoside+ nonnucleosides);

(5) NS3/4A+NS5B(nucleoside);

(6) NS5A+NS5B (nucleoside + nonnucleosides);

(7) NS5A+NS5B (nucleoside);

(8) NS3/4A+NS5A.

Right now, 4 combinations have come out on the market:

(1) NS3/4A+NS5A+NS5B (nonnucleosides) such as Virekira Pak; (2) NS3/4A+NS5B (nucleoside) such as SOF+SMV (3) NS5A+NS5B (nucleoside) such as SOF+DCV, LDV+SOF; (4) NS3/4A+NS5A such as Technivie. And 2 combinations are studied at present: (1)NS3/4A+NS5A+NS5B (nucleoside + nonnucleosides); (2) NS3/4A+NS5A+NS5B (nucleoside). It remains to be seen whether the other 5 combinations can be put on the market: (1) NS3/4A+NS5B (nucleoside + nonnucleosides); (2) NS3/4A+ NS5B (nonnucleosides); (3) NS5A+NS5B (nucleoside+nonnucleosides); (4) NS5A+NS5B (nonnucleosides); (5) NS5B (nucleoside) +NS5B (nonnucleosides). Due to the better effects of the nucleoside analogues towards anti-HCV than that of the nonnucleosides analogues, those combinations are less likely to come out. Among the 3 targets, NS3/4A+NS5A+NS5B (nucleoside + nonnucleosides), the Virekira Pak, was the earliest one to be on the market.

From 2014-2016, there were some variations in the EASL guide towards DAAs. In theTable 1, the treatment using single DAA was PR+NS3/4A (BOC, TVR and SMV). Notably, it should be particularly careful when we apply the NS3/4A targets inhibitor to the decompensated cirrhosis patients. In the meantime, we could also find the therapy of PR+NS5A appearing in the 2014 EASL guide. The PR+SOF and SOF+RBV could be used for the treatment of the different GT patients exposed to HCV. As for the GT 2 patients, choosing the SOF+RBV for 12-20 weeks is optimal. However, it is much better to choose PR+SOF to treat the other HCV patients for 12 weeks. But we should be particularly careful when apply the therapy containing NS5B nucleosideanalogues SOF to the renal insufficiency patients.

Table 1: Anti-HCV therapyrecommended by EASL guide in 2014.

Course (wk)						
Scheme		GT 1	GT 4	GT 2	GT 3	GT 5/6
PR	SOF	12[1]	12[1]	12[1]	12[1]	12[1]
	SMV	24-48	24-48	/	/	/
	DCV	24	24	/	/	/
SOF	RBV	24	24	12-20[1]	24	24
	SMV±RBV	12	12	/	/	/
	SMV±RBV	12-24	12-24	/	12-24	/

[1]Preferred alternative. GT:genotype.

In the Table 2, PR+SO F therapy could also be used for the treatment of the HCV patients with different GT. However, besides PR+SOF, SOF+DCV could also be applied to all the GT patients in the 2015 EASL guide compared with that in 2014. SOF+RBV could only be used for the GT 2 and PR+NS5A was no longer be used. As for the preferred alternative, the therapy in 2014 was the same with that in 2015.

In the Table 3, all the PR treatments were eliminated in the 2016 EASL guide. Single DAA was not recommended. The EASL guide suggested using at least the FDC which contained 2 DAA or other 3 drugs combination to treat the HCV. SOF+DCV and SOF+VEL could be applied to the HCV patients with different GT.

Table 2: Anti-HCV therapyrecommended by EASL guide in 2015.

Course (wk)							
Scheme			GT 1	GT 4	GT 2	GT 3	GT 5/6
PR	SOF		12[1]	12[1]	12[1]	12[1]	12[1]
	SMV		24-48	24-48	/	/	/
SOF	LDV	±RBV	8-24	12-24	/	/	24
3D/r		±RBV	12-24	/	/	/	/
SOF	SMV	±RBV	12-24	12-24	/	/	/
	DCV	±RBV	12-24	12-24	12	12-24	12-24
SOF	+RBV		/	/	12-20[1]	12-20[1]	/
Viekirax	±RBV		/	12-24	/	/	/

[1]Preferred alternative. GT:genotype.

Table 3: Anti-HCV therapyrecommended by EASL guide in 2016.

Scheme			Course (wk)					
			GT 1		GT 4	GT 2	GT 3	GT 5/6
			a	b				
±RBV	SOF	LDV	8-24	8-12[1]	12-24	/	/	12-24
		VEL	12[1]	12[1]	12[1]	12[1]	12-24	12[1]
		DCV	12-24	12[1]	12-24	12[1]	12-24	12-24
		SMV	/	/	12-24	/	/	/
	Virekira Pak		12-24	8-12[1]	/	/	/	/
	Technivie		/	?	12-24	/	/	/
	GZV+ELB		12-16	12[1]	12-16	/	/	/

[1]Preferred alternative. GT:genotype.

4. The existing problems of DAA treatment for anti-HCV.

A. The rapid guide renewal and the drug elimination.

Since 2014, sixguides about anti-HCV therapyhave been released [10-16]. After the guide renewal, many scientists compared the results with relevant literatures and make relevant analysis. No matter how much the guide update, there has not been any first-line treatment.

B. The drug safety.

Drug related instructions have updated many times in 2016. However, most drugs were used beyond the scope of the specification, which caused many side effects such as tiredness, weakness, nausea, anemia and even hepatic failure [17]. In addition, DAA could interact withvarious drugs (drug-drugInteractions, DDI). Table 4 compared the DDI in 2015 EASL guide with that in 2016 EASL guide.

Table 4: The comparison of the drug drug interaction (DDI) in the 2015 EASL and 2016 EASL.

Year	HIV antiretroviral drug	Illegal recreational drug	Lipid-lowering drugs	CNS drugs	Cardiovascular drugs	Immunosuppressor
2015	20	11	11	19	17	7
2016	16	11	11	21	19	7

C. The related HCC.

Previous work [18-20] has shown that the HCV patients treated by DAAs have lower HCC morbidity than those untreated CHC patients. The 51th EASL annual meeting showed that when the HCV patients treated by DAA, the ones with HCC history presented high HCC recurrence rate. So all the cirrhosis patients treated by DAA should be given the close monitoring.

D.The other problems related with DAAs.

(1) For some special patients whose glomerular filtration rateis under 30 mL/min•1.73 m^2 or kidney requires dialysis, there may be some complication when treated by the DAAs or the drug combination containing NS5B [21-24].

(2) For the pregnant woman, patients under 18 or the CHC patients (HBV/HCV co-infected patients), the DAAs therapy should need to be discussed carefully.

(3) For the population of the preexisting resistant mutant strains, the option of choosing other target DAAs is feasible. But for the multidrug resistance towards DAAs, there has not been any therapeutic regimen.

(4) For the decompensated liver cirrhosis or advanced liver disease CHC patients,

theclinical effectsof DAAs on short-term or long-term will await further evaluation.

(5) Researchers are still disagreeing over whether it is should transplant liver before anti-HCV therapy for the decompensated liver cirrhosis patients.

(6) Not all of the counties allow DDAs.

(7) The clinical costs may be another major issue in the anti-HCV therapy using DAAs [25].

4.1 HCV reinfection.

HCV reinfection is still a serious problem for the salvaged HCV patient, especially for the intravenous drug user or the male homosexuality [26-28]. The Interferon-free therapy might ease the possibility of the reinfection. For the CHC patients using DAAs, the reinfection would contribute to the following two reasons. Firstly, because of the short course and the therapeutic convenience, the patients with poor awareness would drown in misdirection and take drugs without doctor's advice [29-32]. Secondly, as the specific antivirals, DAAs would eliminate the major virus strain and the hepatic virus strain. But it is not clear whether DAAs could clear away the extrahepatic virus strain. Therefore, in order to maximize the therapeutic effect, we should not only repeatedly emphasize the risk of reinfection, but also give the professional care [33, 34].

4.2 The HBV reaction for the HBV/HCVco-infected patients treated by DAA.

The treatment of HBV/HCVco-infected patients could refer to that of the patients with single infection of HCV. The sustained viralresponse rate (SVR) of HBV/HCVco-infected patients is similar to that of the patients with single infection of HCV [35,36]. However, the elimination of HCV could cause the action of HBV, which could not be forecasted [37]. So the changing status of HBV DNA should be closely monitored during or after the cure with DAA. We suggested using Tenofovir or Entecavir to treat HBV [38].

5. The obvious changes occurring in EASL for anti-HCV in the recent two years.

The 2015 EASL conference highlighted the following points: (1) The screening of HCV infected patients; (2) The therapy time and the therapeutic schedule of the CHC patients; (3) The interaction between DAAs and other drugs; (4) The therapeutic schedule of the special HCV patients. Unfortunately, this guide did not provide us with the standardized treatment regimen or the first-line treatment regimen.

Compared with the 2015 EASL guide, the guide in 2016 EASL has made some major changes. It reflects in the following five aspects: (1) Given the advantages of the DAAs, the guide recommended all the GT patients infected by HCV adopt the oral medication instead of

the therapy containing IFN. (2) Single DAA was not recommended. The EASL guide suggested using at least the FDC which contained 2 DAA or other 3 drugs combination to treat the HCV. (3) There are two kinds of new drugs: M2 for GT 1/4 and SOF+VEL for all GT. The guide also abandoned the SOF+RBV for GT 2/3 and SOF+SMV for GT 1. (4) Some drugs interactions have been added into the guide such as the Didanosine between DAAs and anti-HIV. In the meantime, the dosage use did not need to be adjusted when using the SOF/LDV and gemfibrozil in the same time. (5) The 2016 EASL guide emphasize the selection of concrete treatment for the HCV patients that need to transplant liver for the first time. But, this guide did not provide us with the standardized treatment regimen or the first-line treatment regimen.

It is worth noting that HCV RNAs do not need to be detected during the therapeutic process for the reason that the therapeutic scheme would not change as the HCV RNA quantification changes. So we do not need to detect the HCV RNAs until the therapy finishes. The final HCV RNAs could be the criterion to decide the further treatment. If there were still HCV RNAs when the therapy ended, we should then take triple DAAs or even DAAs combining IFN to treat the HCV. If none of HCV RNAs are detected, we should detect the HCV RNAs periodically during the treatment stage, especially before treatment and 12 or 24 weeks after treatment. And it is best to testin the same laboratory with same detection method [39-41]. The countries without the detection technology of HCV RNA still use the HCV antibody to judge whether the patients were infected by HCV. However, this method is lack of a certain foundation for the reason that the HCV antibody could still exist sustainably or disappear in part of the patients when the HCV RNA is negative [42, 43].

6. The ideal anti-HCV therapy or DAAs scheme in the future.

(1) Developing an ideal therapy which can be applied to all people. (2) Adopting a much higher treatment in the beginning. (3) The therapy without RBV. (4) The therapy without NS3/4A PI sensitizer. (5) The GT therapy does not need to be detected in the beginning of the therapy. (6) The combination of the non-specific treatment (PR) and the specific treatment (DAA+ RBV).

There are already some scholars at home and abroad studying PR+DAA+RBV. One group in China used danoprevir/r (125/100 mg) and Peg a-2a+RBV to treat GT 1 HCV patients twice a day for 24 weeks within liver cirrhosis patients or 12 weeks within no liver cirrhosis patients. The SVR were all beyond 90% [44]. It could be concluded that the combination of non-specific treatment (PR) and the specific treatment (DAA+ RBV)has broad prospects for development.

7. Conclusion

Based on the above factors, in the late DAA epoch, how to select more reasonable therapy for anti-HCV and make maximization of the patients benefit could still need a further

study. What calls for special attention is that the patients should keep calm and never follow up blindly.

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