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Review Article

Efficacy of current treatments against hepatitis C virus

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ABSTRACT

It is estimated that currently, in the world, approximately 3% of the population has chronic hepatitis, the hepatitis C virus is the etiological agent most related to the development of this pathology. The diversity of genotypes (7) and quasi-species of HCV, due to its high mutation rate, interferes with an effective humoral immunity. The aim of this work is precisely to evoke those usual drugs used in HCV therapy, as well as cutting-edge drugs. The goal of treatment is the eradication of HCV infection. One strategy offered by the WHO is to eradicate the virus in at-risk populations. Alternatives to the previously used treatment with interferon and ribavirin are shown in this paper; protease inhibitors and other targets have now been developed to make eradication of the virus more effective.

Keywords: Hepatitis C virus, Chronic hepatitis, Treatment and drugs

INTRODUCTION

It is estimated that currently, in the world, approximately 3% of the population (about 170 million people) has chronic hepatitis.[1,2-13] The hepatitis C virus (HCV) is the etiological agent most related to the development of this disease.[2,9-17] It is a 9,600 nucleotide, positive-sense, single-stranded, linear RNA virus whose genome is similar in organization to that of flaviviruses and pestiviruses.[1-3] The HCV genome contains a single large open reading frame that encodes a viral polyprotein of about 3,000 amino acids, which is unfolded after translation to generate 10 viral proteins. Its genome encodes core and structural capsid proteins at the 5′ end and five unstructured proteins (including a helicase, protease, and RNA polymerase) at the 3′ end, which are important in viral replication.[1,3,17]

Because HCV does not replicate via an RNA intermediate, it is not incorporated into the host genome.[3] HCV tends to circulate in relatively low titers of 10^3-10^7 virions/ml, so it remains difficult to visualize viral particles of 50 to 80 nm.[1,3] Even so, the replication rate of HCV is very high at 10^{12} virions per day with a half-life of 2.7 h. HCV entry into the hepatocyte is via a non-liver-specific receptor (CD81) and the tightly binding hepatocyte-specific protein claudin-1.[3] A growing list of other host receptors to which HCV binds upon cell entry includes: Ocludin, low-density lipoprotein receptors, glycosaminoglycans, the B1 receptor with phagocytic function, and the epidermal growth factor receptor, among others. HCV, originating from the same mechanism of assembly and secretion of low-density and very low-density lipoproteins, is a lipoviroparticle and masquerades as a lipoprotein, which may limit its visibility to the adaptive immune system and explain its ability to evade immune containment and elimination.[3] Among the host receptors involved in HCV replication are: Cyclophilin A which binds to NS5A and

causes conformational changes necessary for viral replication, and miR-122 host hepatospecific microRNA.[3]

The diversity of HCV genotypes (7, according to some authors) and quasispecies, due to its high mutation rate, interferes with effective humoral immunity.[3,17] Neutralizing antibodies against HCV have been demonstrated, but they are usually short-lived and it has not been proven that HCV infection induces prolonged immunity against reinfection by different viral specimens or even by the same specimen. Therefore, neither heterologous nor homologous immunity appears to arise after acute HCV infection. Some HCV genotypes are present worldwide, while others are more geographically limited.[3] Furthermore, there are differences in genotypes in terms of their responsiveness to antivirals, but not in their pathogenicity or clinical course (except for genotype 3, in which hepatic steatosis and clinical course are more similar).[3]

It is due to the complexity of HCV with the multiple targets with which it interacts to carry out both cell entry and replication within the cell and the fact that chronicity is the rule, since in 84% of cases the acute infection is asymptomatic, that it is necessary to investigate new antiviral and immunomodulatory treatments in the different phases of infection in order to eliminate it and limit damage; and to achieve complete remission in the patient. The aim of this work is precisely to evoke those usual drugs used in HCV therapy, as well as cutting-edge drugs.

THEORETICAL FRAMEWORK

Usual treatment combined with direct-acting antivirals

The goal of treatment is the eradication of HCV[1,8] infection. One strategy offered by the WHO, is to eradicate the virus in at-risk populations.[12,14] Of course, by individualizing the treatment, taking into account the patient's entire environment and physiological characteristics, directly influences the success or failure of treatment.[16] Treatment is completed when there is a sustained virological response (SVR), i.e., no HCV RNA in serum, usually assessed at the end of treatment and 6 months thereafter.[1,3,8,17] SVR is inversely proportional to histopathological activity and risk of progression to cirrhosis.[1,2,8]

Currently, IFN-α and pegylated IFN-α (direct antivirals and immunomodulators) are the mainstay of treatment for chronic hepatitis C.[1-3]

Ribavirin with IFN doubles the SVR, decreasing the relapse rate at the completion of treatment; and even more combined with pegylated IFN-α, as it increases its molecular weight, therefore renal clearance.[1,2] SVR rates with peginterferon plus ribavirin were 45% in patients with HCV genotype 1 and 70-80% with genotypes 2 and 3.[2,3] The current schedule is 48 weeks with PEG IFN-α and ribavirin in patients with genotypes 1 and 4. In genotypes 2 and 3, 24 weeks of PEG IFN-α and ribavirin are used. In the 4 genotypes already mentioned, when there is relapse, treatment is repeated at higher doses as well as prolonged and bone marrow support is sought with filgastrim or erythropoietin.[1,3]

The use of peginterferon has disruption rates of 15-30% because it is accompanied by distressing side effects.[2,3.]

First-generation protease and HCV polymerase inhibitors avidly reduce HCV RNA levels.[1,2] Adding boceprevir to peginterferon alfa and ribavirin achieves SVR against genotype 1 in 24 weeks.[2,3]

NS5A inhibitors have high antiviral potency at picomolar doses. Ledipasvir has potent activity against genotypes 1, 4, 5 and 6, and together with sofosbuvir is highly effective in treating patients with or without prior treatment, including those with cirrhosis. The duration is 12 weeks in patients infected with genotype 1 with cirrhosis and previous treatment, and 24 weeks in cirrhotic patients without previous treatment.[2,3,17] It is shortened to 4 weeks when there is no cirrhosis or previous treatment, in addition to an SVR less than or equal to six million IU/ml in the initial stage.[2] When HIV patients are co-infected with genotype 1 and the treatment regimen of ledipasvir and sofosbuvir is used, they achieve SVR rates greater than 90%.[2] A study in Africa showed SVRs of up to 95%.[13] Something that represents a problem with these drugs are polymorphisms in NS5A, the most common being the double substitution in L28V and L30R, for these cases flecaprevir can be added with pibrenastavir.[5,19]

When genotype 3 is present, the combination of ledipasvir, sofosbuvir and ribavirin achieves high SVR rates.[2]

Non-nucleoside polymerase inhibitors are the weakest class against HCV; most of the drugs in this class have more activity against genotype 1b.[3,2] Many people infected with genotypes 2 or 3, including those coinfected with HIV, are cured with 12 or 24 weeks of treatment, respectively.[3]

No resistance has been observed with concomitant use of sofosbuvir with any drug. The combination of sofosbuvir and simeprevir is effective in genotype 1 infection. On the one hand, genotype 1 is cured with SVR greater than 90%; on the other hand, genotype 2 infection with cirrhosis is the most difficult variant to treat.[2]

Since 2013, a trend began with the use of antiviral drugs against HCV of OV, interferon-free, this are well-tolerated, non-resistance- generating, single-dose, pangenotypic, 8–12-week duration, and SVR >95%, with a duration ranging from 8 to 12 weeks.[8,3] Both simeprevir and sofosbuvir are effective against genotype 1, however, the second one is considered pangenotypic, yet they have been replaced by interferon-free oral drugs.[3,8,15,17]

Regarding simeprevir with PEG IFN, its efficacy has been truncated due to its multiple drug interactions and adverse effects; the combination of simeprevir and sofosbuvir for 12 weeks is effective in all types of patients. It is less effective in individuals with resistance and cirrhosis, as it achieves only 79% SVR, in contrast to the 97% SVR achieved by patients without previous treatment; the diversity of SVR in other types of patients fluctuates between these two extremes.[17]

Sofosbuvir has high potency, high resistance barriers, pan-genotypic activity, is well tolerated, with limited side effects, and is almost free of major drug interactions.[17]

Nowadays, sofosbuvir is used in combination with simeprevir, or more often with an NS5A inhibitor.

The sofosbuvir machinery with ledipasvir in the treatment of all types of patients achieved an SVR between 97% and 99%. Treatment always ranged between 86 and 100 percent; depending on the corresponding comorbidities of the patients (3). This combination is equally effective for patients with HIV co-infection in both decompensated cirrhotics and post-transplant patients, and has few drug interactions.

There has been research about paritaprevir, ritonavir, ombitasvir, and dasabuvir, and it has been registered that the combination of ritonavir with paritavir and ombitasvir generates SVR of 94%-100% in genotypes 1 and 4 in all types of patients. It is an excellent option in patients with renal failure. Although highly effective, a major trade-off is that they induce hyperbilirubinemia and hepatotoxicity, so caution must be exercised in decompensated cirrhosis. Compared to sofosbuvir/ledipasvir, this regimen has the disadvantage of requiring treatment with ribavirin c/12 h for genotype 1a and is contraindicated in decompensated cirrhosis.

Sofosbuvir and daclatasvir: Although the data for genotype 3 are more robust, clinical studies of this combination in genotypes 1 and 2 support its efficacy and its recommendation as first-line treatment (genotype 1) and as an alternative treatment (genotype 2), in some cases in combination with ribavirin. The SVR rate achieved with this therapy is 92 to 98%, except in genotype 3 which was 89%. Unfortunately, the results for genotype 3 patients with progression to decompensated cirrhosis have been unfortunate, with SVR not exceeding 56%. The combination of daclatasvir-sofosbuvir should be the treatment of choice for genotypes 1 and 3 and is recommended as an alternative for genotype 2. Its efficacy has been studied in patients with comorbid cryoglobulinemia, demonstrating an SVR of 76%.[10]

Moving on with the combination of elbasvir/grazoprevir, it hits genotypes 1 and 4; averaging 95.5% SVR in all types of patients. This combination is as effective in patients with HIV-HCV coinfection as it is in patients with advanced renal failure (including those requiring hemodialysis); it is contraindicated in decompensated cirrhosis. Compared to other available regimens for genotypes 1 and 4, elbasvir/grazoprevir has the disadvantage or drawback of requiring baseline NS5A polymorphism testing, but has the advantage of a comparable regimen for cirrhotics and non-cirrhotics, for treatment of patients with and without prior treatment, and for patients with normal renal function or renal failure.

Sofosbuvir/velpatasvir: these are used against genotypes 1-6 for the treatment of cirrhotic and non-cirrhotic patients with or without prior treatment.[3,8] No ribavirin is required, which includes patients with genotypes 2 and 3, with the exception of patients with decompensated cirrhosis. Reaching an average of 98.5% in all genotypes, except genotype 3, where it was 95%. In addition, it is possible to do without quantifying the baseline NS5A polymorphism.[3,8] As with other sofosbuvir-containing regimens, the sofosbuvir/velpatasvir combination should not be administered with amiodarone (potential for severe bradycardia); in addition, P-gp inducers and moderate to potent CYP3A inducers may reduce plasma concentrations of sofosbuvir and/or velpatasvir. These drugs have been shown to be effective in patients injecting drugs parenterally.[9,18]

One drug that has been studied, and will not be mentioned here, is interferon lambda-3 (2).

State of the art treatment

"Vanguard" will be taken as drugs emerged from 2017 to the day this text is written.

Most treatments need to meet the current DAA regimens described above; however, several highly potent pan-genotypic drug combinations are in development. For example, an investigational protease inhibitor (voxilaprevir) added to a polymerase inhibitor/NS5A inhibitor combination such as sofosbuvir/velpatasvir results in a well- tolerated triple drug combination with SVRs of 97%-98% in all HCV genotypes and patient subgroups. This includes cirrhotic/non-cirrhotic, previously treated and untreated patients, including those treated with NS5A inhibitors and results were independent of the number of DAAs received and no effect on baseline NS5A SARs was observed. Various experimental combinations may allow for longer treatment durations.[3,8,18]

In a small exploratory study, a six-week combination of sofosbuvir plus an experimental highly potent, low-resistance pangenotypic drug from the NS5A inhibitor group (odalasvir) achieved SVR in 100% of 12 patients with genotype 1 infection. Similarly, a six-week triple combination including odalasvir with simeprevir, a protease inhibitor 89 and an experimental polymerase inhibitor ("AL-335"), had a 100% SVR in 20 previously untreated non-cirrhotic patients with genotype 1 infection. In Phase II clinical studies, eight weeks of an experimental

combination of 2 highly potent pangenotypic drugs, a protease inhibitor ("ABT-493") plus an NS5A inhibitor ("ABT-530"), the addition of voxilaprevir in non-cirrhotic patients with no previous treatment, had 100% SVR in genotypes 1, 2 and 3. In cirrhotics with genotype 3 and in patients with genotypes 4, 5 and 6, treatment for 12 weeks with direct-acting antiviral combination had an SVR12 of 100%. In patients with a history of DAA treatment failure, 12 weeks of this dual combination was sufficient to achieve SVR12 ≥95%; no influence on SVR rates of baseline SARs or baseline NS5A was observed. No safety concerns were found and the potential for drug-drug interactions is limited. These promising combinations are in phase II and III clinical trials.[3,8]

Less advanced is the development of host protein inhibitors, such as non-immunosuppressive inhibitors of cycloserine A (which interact with NS5A during HCV replication) and subcutaneously administered non-coding antagonists of liver-expressed microRNA-122 (which promotes HCV replication). Given the accelerated progress of orally administered DAAs, with treatments of short duration and high efficacy, these alternative methods may not be practical or competitive; the development of both methods has been delayed by the emergence of toxic effects such as cycloserine inhibitor-associated pancreatitis and microRNA-122-related jaundice.

Although data regarding the impact of DAAs on the natural state of chronic hepatitis C are still limited, preliminary data indicate that successful treatment is associated with gradual reduction in fibrosis progression and regression of advanced fibrosis (cirrhosis), improved survival in patients with decompensated cirrhosis, and a decrease in the number of patients with hepatitis C referred for liver transplantation. Based on the known prevalence, progression and rate of progression of chronic hepatitis C and the efficacy of DAA treatments and their impact on hepatitis C complications, estimates have suggested that the availability and application of these treatments have the potential to reduce the burden of hepatitis C-related disease, including liver-related death, HCC, decompensated cirrhosis and liver transplantation by 50 to 70% between 2015 and 2050.

Table 1: Medications used in HCV therapy.

Drugs	Mechanism of action	HCV genotype	Adverse effects
IFN-α	Induces cells to a state of resistance to viral infections	-	Aches, pains, general discomfort, and low blood cell counts
Pegylated IFN-α	Antiviral, antiproliferative and immunomodulatory mechanisms	-	Anorexia, depression, insomnia, generalized pain and flu like symptoms
Ribavirin	It is incorporated into the RNA chain inhibiting its elongation[4]	1, 2, 3, 4[4]	Hemolytic anemia, reticulocytosis, insomnia, irritability and depression
Boceprevir	NS3/4A protease inhibitor[6]	1	Anemia, neutropenia, dysgeusia, fatigue, nausea and headache.
Ledipasvir	NS5A inhibitor	1, 4, 5, y 6.	Fatigue, headache, insomnia, nausea and diarrhea.
Sofosbuvir	NS5B inhibitor[7]	1, 2, 3, 4, 5, 6[7]	Fatigue, headache, insomnia, and nausea[7]
Simeprevir	NS3/4A inhibitor[11]	1, 2, 4, 5 y 6[11]	Erythema and photosensitivity
Paritaprevir	NS3/4A inhibitor[20]	1a and 1b[20]	Tiredness, weakness, hyporexia, nausea and vomiting[20]
Ritonavir	Inhibitor of Paritaprevir metabolism by CYP34[20]	1a and 1b[20]	Tiredness, weakness, hyporexia, nausea and vomiting[20]
Ombitasvir	NS5A inhibitor[20]	1a and 1b[20]	Tiredness, weakness, hyporexia, nausea and vomiting[20]
Dasabuvir	NS5B inhibitor[20]	1a and 1b[20]	Tiredness, weakness, hyporexia, nausea and vomiting[20]
Daclatasvir	NS5A inhibitor[7]	1, 2, 3, 4[7]	Fatigue, headache, insomnia, and nausea[7]
Elbasvir	NS5A inhibitor	1a, 1b and 4	Headache and tiredness
Grazoprevir	NS3/4A inhibitor	1a, 1b and 4	Headache and tiredness
Velpatasvir	NS5A inhibitor[20]	1, 2, 3, 4, 5, 6[20]	Headache and tiredness[20]

DISCUSSION

The main objective of our bibliographic review was to show which pharmacological treatments are considered suitable nowadays to treat the pathology caused by the hepatitis C virus, furthermore to evoke those drugs that were thought to be optimal against this pathogen.

The authors of this text consider the issue of selecting the right antiviral drug of vital importance, because choosing the therapy to be used in a patient is the turning point in what kind of quality of life will take, or if it will take one at all. Today it is estimated that 3% of the world has this virus in their systems, which more or less would be about

170 million individuals distributed around the globe, if we put them together in the Mexican national territory, it would exceed by 50 million people with hepatitis C virus the number of inhabitants of Mexico in 2015, in other words; many people suffer from this potentially fatal ailment.

According to WHO data published on its website, 399,000 people die every year due to cirrhosis, hepatocellular carcinoma, and other complications caused by HCV. We maintain that, even if there was only one patient with this condition, it would not be less important to invest efforts in employing the correct chemical compound, however, the situation distresses the health of 3% of humanity, and virtually a growth of the statistics of the population infected by this small RNA virus.

For all the arguments presented above, we justify the need and the importance of this paper.

Regarding the bibliography selected for the elaboration of this work, we found it refined, each one of the articles that compose it, whether they are bibliographic review or experimental studies, have the necessary methods for their correct task. Regarding the "confrontation" of the information at the moment of making this "collage" of bibliographic sources, we did not find discrepancies, instead some of them validated the others, and vice versa, but varied in what specific sample of the population they used to evaluate the medicines. Properly speaking, it would not be appropriate to raise the information in the text in this section-discussion-because the central thesis of this paper is not to confront or compare information, but rather to present hard data on the efficacy of these anti-HCV drugs.

CONCLUSION

The treatment of a disease with such a high prevalence and with a distribution around the world, such as chronic hepatitis C is, has been part of the priority agenda of the medical institutions, thus achieving a diversity of drugs that delimit its damage and contribute to the welfare of patients. The gradual understanding of the HCV life cycle and its way of generating pathology has culminated in the development of drugs with a broader spectrum against its genotypes and a more refined action against them that subtracts in negative side effects and adds in obtaining reassuring sustained viral responses. Humanity is definitely approaching the WHO's objective of eradicating this small RNA virus, and the medical advance has been indispensable, however, it has to go hand in hand with an improvement of the methods of early diagnosis, because if the genesis of the problem is not known, little or nothing can be done to solve it. Through the research for the writing of this document, we understood that the accumulated knowledge leads to the acceleration of progress, because, like the footprints on the beach, they help us not to repeat the path and to keep moving forward.

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