

Hepatitis C: review of the drugs used for treatment

Hepatite C: revisão dos medicamentos utilizados no tratamento

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ABSTRACT: The objective of this work was to conduct a review of the literature on the drugs used for treatments of the hepatitis C since the discovery of the virus in 1989. In order to reach this goal a search was made at the bases Medline and SciELO using the terms “*hepatitis C*”, “*treatment*”, “*interferon-free*”, “*review*” and “*clinical trial*”. This work presents a review of the general characteristics of hepatitis C together with its epidemiology and diagnosis. For a long time, the only option available for the treatment of hepatitis C was interferon. This drug did not show good efficacy and its use was minimized with the emergence of new interferon-free regimens that increased the success rate to somewhere around 95%. Such drugs have allowed the actual reach of virus cure, although they are available in Brazilian Single Health System (SUS), they are expensive treatments that restrict access to much of the infected population.

keywords: Hepatitis C/therapy; Hepatitis C/diagnosis; Hepatitis C/drug therapy; Interferons; Review literature as topic.

RESUMO: O objetivo deste trabalho foi realizar uma revisão da literatura sobre os fármacos utilizados para o tratamento da hepatite C desde a descoberta do vírus, em 1989. Para atingir esse objetivo, foi realizada uma pesquisa nas bases Medline e SciELO, utilizando o termos “*hepatite C*”, “*tratamento*”, “*livre de interferon*”, “*revisão*” e “*ensaio clínico*”. Este trabalho apresenta uma revisão das características gerais da hepatite C juntamente com sua epidemiologia e diagnóstico. Durante muito tempo, a única opção disponível para o tratamento da hepatite C foi o interferon. Esta droga não mostrou boa eficácia e seu uso foi minimizado com o surgimento de novos regimes sem interferon que aumentaram a taxa de sucesso para algo em torno de 95%. Tais medicamentos permitiram o alcance real da cura do vírus, embora estejam disponíveis no Sistema Único de Saúde (SUS) brasileiro, são tratamentos caros que restringem o acesso a grande parte da população infectada.

Palavras-chave: Hepatite C/terapia; Hepatite C/diagnóstico; Hepatite C/tratamento farmacológico; Interferons; Literatura de revisão como assunto.

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INTRODUCTION

Viral hepatitis are transmittable infectious diseases that due to his high mortality, are actually a big public health issue. Among viral hepatitis, hepatitis C is the most common cause of hepatic transplantation due to high severity. It is a slow evolution disease with a high chronicity rate, turning into a potentially fatal condition in comparison with other viral hepatitis¹⁻³.

Currently there are around 170 million people infected with hepatitis C virus (HCV). These people are likely to develop cirrhosis or hepatocellular carcinoma (HCC). Unfortunately, every year, liver diseases kills approximately 350,000 lives^{4,5}.

METHODOLOGY

This is an exploratory and narrative bibliographical study. Were performed a search in Scielo and Medline database using the terms “hepatitis C”, “treatment”, “interferon-free”, “systematic review” and “clinical trial” until February 2018, considering original studies and revisions. There were identified 172 articles from the defined search criteria. Two reviewers select 117 articles for reading and information extracting. To compose this study, only 60 articles were used.

LITERATURE REVISION

The viral hepatitis

The first report available in scientific literature, which may even indirectly relate to hepatitis, are found in Chinese’s manuscripts dated about five thousand years ago, which refer to the appearance of jaundice in the population. The term hepatitis was only introduced in the seventeenth century by Bianchi in the scientific work called “*Historia hepática sem thoria et praxis omnium morborum hepatitis et bilis*” published in 1725⁷. Only in 1989, after researches involving cell biology, Choo et al.⁶¹ identified the genome of an alleged viral agent responsible for 90% of non-A and non-B post-transfusion hepatitis, which they denominate as hepatitis C virus, with own characteristics that distinguish it from other hepatotropic viruses⁶⁻⁸.

The most known liver viruses are hepatitis A virus (HAV), E (HEV), B (HBV), C (HCV), D (HDV). The first two are transmitted by fecal-oral route, and the others parenterally^{9,10}.

Hepatitis C

Hepatitis C was for years a disease without etiological agent known. The causative agent of non-A and non-B post-transfusion hepatitis was not known, remaining a doubt among researchers. The understanding

of this mystery came only in the 1980s when Choo et al.⁶¹ classified hepatitis C virus in 1989 belonging to *flaviridae* family and *hepacivirus* genus whose transmission is by blood or blood products¹¹.

HCV has the genomic structure of RNA, and encodes a polyprotein with approximately three thousand amino acids, which gives rise to the capsid protein (C), two envelope proteins (E1 and E2) and other non-structural proteins (NS1, NS2, NS3, NS4A, NS4B, NS5A and NS5B). There are approximately 11 genotypes and around 80 subtypes, due to this genomic variability coupled to high virus mutation rate, the population infected is extremely heterogeneous, which facilitates viral survival in response to attacks of the host immune system^{3,12-15}.

Among the disease’s stages, they are classified in acute and chronic period. In the acute stage, many patients are asymptomatic despite the high amount of circulating viral RNA in the first six months of infection. However, many experience symptoms like fever, fatigue, malaise, anorexia, nausea, dark urine and yellowish eyes. Such symptoms may appear 3 to 12 weeks after infection³.

Approximately 85% of acute patients evolved to chronic state, where the main manifestations of the disease are due to chronic inflammation in the liver, resulting in fibrosis and can progress to cirrhosis within 20 years, which may lead to functional loss if decompensated. Worsening prognosis’s main alternative is liver transplantation^{16,17}.

Patients with cirrhosis often develop hepatocellular carcinoma, which lead 20% of these patients to die. Another important fact is besides bringing several injuries to the liver, hepatitis C causes several systemic disorders such as: cryoglobulinemia, chronic lymphocyte stimulation, Sjogren’s syndrome, lupus erythematosus, insulin resistance and diabetes mellitus in addition to a series of rheumatological, dermatological and endocrine changes¹⁸⁻²¹.

Geographical distribution of the virus

Although hepatitis C is considered a pandemic, its geographical distribution is heterogeneous. In developed countries, HCV prevalence is low at about 2% among adult population, while in less developed countries the rate is around 10%. Countries with the highest prevalence are those located in Asia and Eastern Mediterranean, Africa and Western pacific; areas with lower prevalence compass North America, Western Europe and Australia⁵.

The genotype distribution and the prevalence varies around the world. Among the 6 genotypes identified (1, 2, 3, 4, 5 and 6), genotype 1 is the most prevalent. Responsible for about 50% of all infections, it is also the most difficult type to achieve cure or remission with the standard of treatment with pegylated interferon (IFNpeg) associated with ribavirin (RBV)^{22,23}.

Subtypes 1a, 1b, 2a, 2b, 3a are all found in Brazil, Western Europe and United States. Genotype 3 is most common in India, Bangladesh and other parts of Asia. In North Africa and the Middle East (mainly Egypt) there is a predominance of genotype 4. Finally, genotypes 5 and 6 are found in regions of South Africa and Asia, respectively^{11,24}.

Transmission and diagnosis

Several studies^{1,2,4,25} point out that main risk factors for contamination include blood transfusions and blood products, injecting drug users, hemodialysis, occupational exposure to blood, people with multiple sexual partners, HCV positive mothers and perinatal transmission. Some procedures such as tattoos, piercings, acupuncture and sharing of personal hygiene items can also be important contamination pathways²⁵.

Regarding the diagnosis of hepatitis C, it is performed through two types of tests: direct and indirect. Indirect assays are used to detect anti-HCV antibodies, and direct assays are used to verify the presence of viral RNA in serum samples using polymerase chain reaction^{26,27}.

Treatment until 2011

Among chronic diseases, we have had the possibility of achieving a cure for hepatitis C with new drugs. However, some side effects were important and serious, as well as not affecting the progression of end-stage liver disease to hepatocellular carcinoma²⁸.

In theory, the goal of antiviral treatment is to achieve sustained virological response (SVR) defined as undetectable antiviral RNA 12 weeks after the end of treatment. Thus, taking into account this parameter, patients are generally considered cured when they reach SVR. These patients have an improvement in prognosis with prevention of cirrhosis-related morbidity and mortality and a better histological result with 30% reduction in all-cause mortality. It should be remembered that some host factors as age greater than 40 years, male individuals and race are limiting agents in achieving SVR²⁹⁻³².

Even before the discovery of HCV, non-A and non-B hepatitis was treated with interferon alpha, discovered in the United States in 1992. This drug had an efficacy between 5-20% with relevant effects on serum transaminases and SVR. Patients had to take three weekly injections with a standard treatment between 24 to 48 weeks and the results were not satisfactory. It is interesting to note that at the time the reach of SVR with IFN greatly reduced the incidence of hepatocellular carcinoma. However, its efficacy and safety were not satisfactory besides treatment failures and patients who did not tolerate it well^{14,33}.

Considering the problems related to the use of interferon alpha, in 2001 there was a change in its structure, in which a polyethylene glycol molecule was added. This

structure was called pegylated interferon (IFNpeg). There was a pharmacokinetic optimization that enabled higher and longer lasting serum concentrations to act with constant pressure on the virus. In addition, this optimization allowed a one injection per week³⁴⁻³⁶.

But what are interferons? In general, interferons are a group of naturally produced proteins with immunoregulatory function. In mammals it is verified that there are more than ten species of interferons with antiviral activity. They are classified into 3 groups: type I, II and III. Type I interferons comprise interferon alpha and beta. Type II has only one representative: interferon gamma. Type III comprise the lambda interferons (1,2 and 3) frequently presented as IL29, IL28A, IL28B respectively^{37,38}.

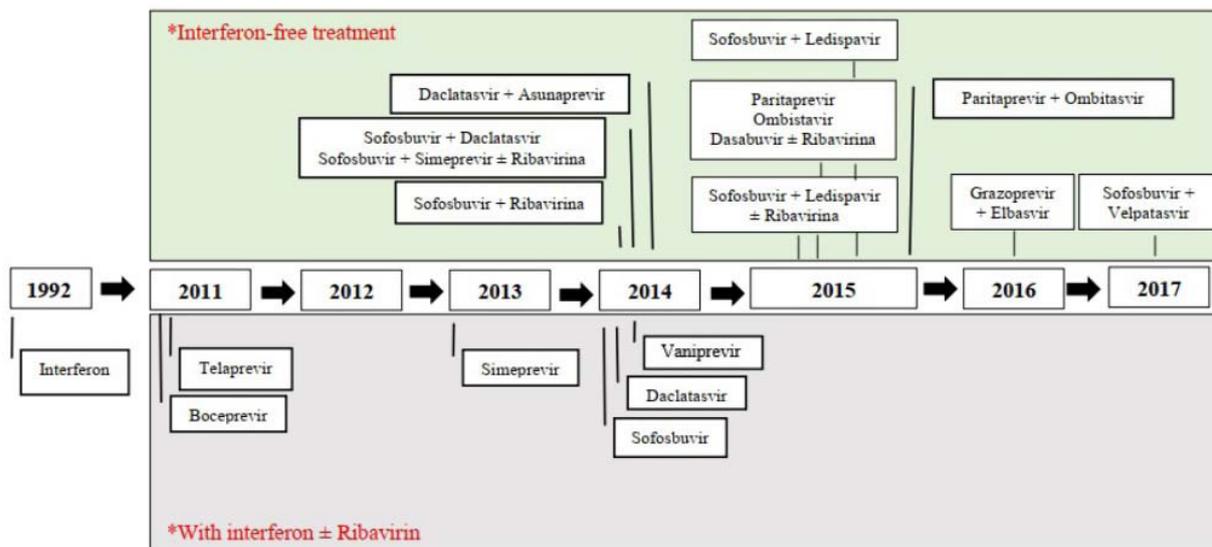
When there is a viral infection, interferons are produced by certain cells and inhibit the synthesis of DNA and RNA. In patients with hepatitis C, for example, hundreds of interferon-stimulating genes are expressed in hepatocytes. Thus, this innate response allows a reduction of the HCV viral load that may result in greater effectiveness of CD4 and CD8 lymphocytes³⁹.

Understanding this defense mechanism via interferon is fundamental because in hepatitis C, patients with the favorable genotype IL28B homozygous for the rs12979860 allele (CC genotype) are more likely to achieve sustained virological response with the IFNpeg/RBV treatment (around 69%) than heterozygous patients (CT) or homozygous for rs8099917 (TT genotype) allele^{34,40-43}.

Given the importance of interferons, it is important to keep in mind that the available treatment for hepatitis C until 2011 followed the combination of IFNpeg2a/2b associated with Ribavirin for 24 weeks (for genotype 2 and 3) or 48 weeks (for genotype 1 and 4) based on sustained virological response at 4th and 12th week. This therapy, however, reached an SVR only in 50% of the patients infected with genotype 1 besides having some important contraindications such as decompensated liver disease, renal and cardiovascular problems. It is worth mentioning the success of this treatment depends on the genotype, viral load and type of IL28B host genotype (if CC, CT or TT)^{14,35,44-46}.

Also in 2011, there was an increase in antiviral therapy for hepatitis C with the emergence of a new class of drugs called direct acting antiviral agents (DAA). The first representatives of this class are called protease inhibitors (PIs), being Boceprevir (BOC) and Telaprevir (TVR) the two most important members. Both are used for the treatment of genotype 1, since this genotype was very difficult to treat with standard IFNpeg plus RBV treatment. From then, the possibility of triple therapy appeared, combining a PI plus IFNpeg and RBV (Figure 1). PIs provided a more chance of cure since SVR rate increased from about 50 to 75%^{23,47-49}.

Figure 1. Hepatitis C drug timeline



Drug therapy after 2011

With a better understanding of HCV viral cycle, was possible with DAAs to direct the treatment to specific targets involved in viral replication. However, the use of interferon alpha was still necessary, even with side effects (fatigue, insomnia, headache, nausea and depression). With new research in continuity, two new drugs were approved in 2013: simeprevir and sofosbuvir⁵⁰.

With these new drugs SVR reached 95%. Another relevant factor that brought benefits to the patient was the availability of Fibroscan® equipment, an ultrasound device with good diagnostic acuity in the presence of cirrhosis, which was a good option for cases requiring hepatic biopsy⁵¹.

In addition to the first generation PIs, nucleotide inhibitors, non-nucleotide inhibitors of the NS5B complex and NS5a inhibitors also appeared. These drugs target other fractions of the polyprotein synthesized by HCV and their use is promising because they allow interferon-free treatment regimens for patients with hepatic cirrhosis or with a high degree of hepatic decompensation^{37,52-55}.

The main weaknesses of first-generation DAAs are low resistance to genetic variation of HCV and limited efficacy to genotype 1. The second generation circumvented this problem by broadening the spectrum of treatment for the other genotypes (Table 1) in addition to more appropriate doses and increase in tolerance and safety. Interferon-free therapies have addressed most of the problems encountered in the course of HCV infection. Although the introduction of DAAs into the drug regimen is desirable, some barriers such as the high cost and access restriction to these drugs can be considerable obstacles^{29,56-58}.

Concerning interferon-free regimens, the clinician should also be aware of drug interactions that may occur

with other ongoing treatments that use statins, proton pump inhibitors and some antibiotics. It is extremely relevant that each patient is rigorously evaluated and monitored to identify any important event during therapy²⁶.

But effective medicines are not enough. Effective public policies are also needed among injecting drug users, the main reservoirs of HCV. What we observe is that such policies do not have the desired effect and perhaps the best strategy for controlling infection would a prophylactic vaccine development.

But what has been found in the studies so far developed is that some vaccines in the test phase, despite inducing strong humoral and cellular immune responses in preclinical animal models or in clinical studies with humans, they have not been approved for use in human beings^{3,59, 60}.

HCV has high genetic variability associated with differences in disease progression and efficacy of antiviral treatment. Nowadays, hepatitis C counts more affected than the human immunodeficiency virus (HIV), however the majority of cases remain underdiagnosed. That is why the public health system needs measures focused on early diagnosis and prevention.

Therefore, even with numerous benefits derived from the development of new drugs in recent years, they are still expensive, which constitutes a barrier in the access of a large part of the population. In addition, the idea of a prophylactic vaccine against HCV is only a future perspective. What seems to be the best option is to reduce virus exposure through prevention. Such reduction can be achieved by monitoring blood donors, increasing safety in medical procedures, promoting counseling for populations at-risk and broadening HCV testing³.

Table 1. Direct acting antiviral drugs

Class	Generation/wave	Generic name	Codified name	Commercial name	Manufacturer	Genotypic action	Medical combination
NS3/4A inhibitor	First generation/ first wave	Telaprevir	SCH503034	Incivek®	Merck	1	Combined with pegylated interferon and ribavirin
		Boceprevir	VX-950	Victrelis®	Janssen	1	Combined with pegylated interferon and ribavirin
	First generation/ second wave	Simeprevir	TMC-435	Olysio®	Tibotec	1,4	Combined with sofosbuvir
		Asunaprevir	BMS-650032	Sunprevia®	BMS	1,4	Combined with pegylated interferon and ribavirin or daclatasvir
		Paritaprevir	ABT-450/r	Technivie®	AbbVie	1,4	Combined with ritonavir and ombitasvir
	Second generation	Grazoprevir	MK-5172	Zepatier®	Merck	1,4	Combined with elbasvir
		Voxilaprevir	GS-9857	Vosevi®	Gilead	1,2,3,4,5,6	Combined with sofosbuvir and velpatasvir
		Glecaprevir	ABT-493	Mavyret®	AbbVie	1,2,3,4,5,6	Combined with Pibrentasvir
	NS5A inhibitor	First generation	Daclatasvir	BMS-790052	Daklinza®	BMS	1,3,4
Ledispavir			ABT-450	Harvoni®	Gilead	1,3,4	Combined with sofosbuvir
Ombitasvir			ABT-267	Viekira XR®	AbbVie	1,4	Combined with paritaprevir, ritonavir and dasabuvir
Second generation		Elbasvir	MK-8742	Zepatier®	Merck	1,4	Combined with grazoprevir
		Velpatasvir	-	Epclusa®	Gilead	1,2,3,4,5,6	Combined with sofosbuvir
NS5B inhibitor	-	Sofosbuvir	GS-7977	Sovaldi®	Gilead	1,2,3,4,5,6	Combined with daclatasvir
		Dasabuvir	ABT-333	Viekira XR®	AbbVie	1,4	Combined with ombitasvir, paritaprevir and ritonavir

FINAL CONSIDERATIONS

For decades HCV was ahead of the researchers. The effort to develop more efficient drugs was not able to suppress the virus ability to form resistant strains to the treatment.

Treatment based on the combination of nonspecific drugs such IFNpeg resulted in numerous side effects besides treatment being long-lasting and with little success in patients infected with genotype 1. The cure rate observed at baseline was less than 50% and the treatment had high toxicity. For this reason, much effort was invested in the development of new drugs against HCV which led to the approval of first generation DAAs, called generically protease inhibitors. This provided triple therapy that achieved cure rates of about 70% in treatment naïve patients. Although the addition of these new drugs marked a new era with improved prognosis, the side effects were still intense beyond a wide drug interaction.

The advantage of the researchers came understanding the viral replication system, which enabled the development of new drugs capable of ceasing virus multiplication. In addition, the introduction of DAAs allowed several

treatment combinations (associated or not with ribavirin) to achieve cure in more than 90% of patients. The safety and efficacy profile of these new combinations are particularly important in difficult-to-treat patients, notably those with advanced liver disease and those with recurrent infection following liver transplantation.

There are a large number of DAAs under development and the obtained results in clinical trials are grounds for optimism among professionals treating HCV patients. Thus, currently available HCV treatments are satisfactory since most drugs have reduced toxicity and better pharmacokinetic profiles in addition to satisfactory bioavailability. It is a consensus that the ideal combination of DAAs should include potent efficacy, high genetic barrier to resistance, pan genotype coverage, few side effects and a good safety profile, while secondary characteristics should include few doses during treatment, no dietary restriction, low drug interaction and low cost.

Finally, despite high cost of some medicines, Brazil offers the latest generation of medicines for population through the Single Health System (SUS) for free. Thus, according to the Clinical Protocol and Therapeutic Guidelines for Hepatitis C prepared by the Ministry of

Health, the following drugs are now available through SUS: Dactacastavir, Simeprevir, Sofosbuvir, Ombistavir/Dasabuvir/Veruprevir and Ritonavir combination, Ledispavir/Sofosbuvir association and Elbasvir/Grazoprevir

combination. Current medications also allow treatment of patients coinfecting with HIV to be performed analogous to HCV-monoinfected. In addition, pre or post-transplanted patients are adequately cared in order to improve quality and life expectancy.

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