Future perspectives in the treatment of chronic Hepatitis C

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ABSTRACT

The main lines of research into new drugs and treatment strategies against type C viral hepatitis are described. This disease is a major public health problem, with more than 700,000 people affected by the illness in Spain and with a high degree of prevalence amongst prison inmates. Limitations on current treatment for viral hepatitis C have led to research into new drugs in the form of two main product lines, some of which are soon to be available on the market: NS3/4ª serine-protease inhibitors (telaprevir, boceprevir, danoprevir and vaniprevir) and the NS5B RNA polymerase inhibitors (RG-7128, RG-7227, Filibuvir, ANA-598). The latter are in a somewhat earlier stage of development. It is expected that these new drugs will have to be used alongside the current standard treatment of pegylated interferon plus ribavirin and under these conditions of use the new drugs have already shown greater effectiveness than the current standard treatment. Despite this encouraging perspective, the new medicines have limitations such as the development of resistances, toxicity, and the little knowledge available of their effectiveness on viral genotypes that are different from 1. That being said, their appearance opens up new possibilities in the treatment of this disease.

Key words: hepatitis C; therapeutics; Pharmaceutical Preparations; biomedical research; toxicity; public health; prisons; Spain.

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INTRODUCTION

Chronic infection by the Hepatitis C virus (HCV) is a major public health problem, with approximately 175 million people infected worldwide. It is estimated that the prevalence of chronic hepatitis C amongst Spanish population ranges between 1.5 and 2.5%. Prevalence is greater amongst prison population, due fundamentally to a history of Injection Drug Use (IDU) in a relatively high number of inmates. The existence of common routes of infection with HIV makes HIV-HCV co-infection to be high amongst prison population with a history of IDU. After many years, chronic infection with HCV is associated with a higher incidence of hepatic cirrhosis and hepatocellular carcinoma.

At present, and since there is no vaccine against HCV, the treatment of chronic hepatitis C is based on the combination of pegylated interferon-alpha (peg-IFN) and ribavirin (RBV). Nevertheless, seeing that it is less effective on certain groups of patients (e.g.: HCV genotype 1 and 4, co-infection with HIV) and that adverse effects are frequent, new antivirals against HCV are in final stage of clinical development. They are called DAA (direct acting antivirals) and are primarily polymerase inhibitors or HCV protease inhibitors.

EPIDEMIOLOGY

More than 700,000 people have chronic HCV infection in Spain[1], which is an intermediate prevalence rate, in line with that of most Western European countries. Prison inmates in Spain show prevalence rates of chronic infection that are significantly higher, up to 25 % higher in a study[2]. Over the last decade, and on account of the implementation of diseases prevention and control programmes in prisons, together with harm reduction and health promotion programmes, this prevalence has diminished considerably since figures close to 50% at the end of the 1990's. Similarly, rates of HCV seroconversion in Spanish prisons have diminished from 5% in 1998 to 1.5% in 2008.

With respect to the distribution of HCV genotype, a study of 800 inmates carried out in a Spanish prison[3] revealed the predominance of genotype 1 (51%) in comparison to 30 % of patient with genotype 3 or 17 % with genotype 4.

CURRENT THERAPEUTIC REGIMENS

There is at present a general consensus about the efficacy of combining peg-IFN and RBV for the treatment of chronic hepatitis C. Multiple studies have shown the superiority of treatment with Peg-IFN α-2a or α-2b over standard interferon or Peg-IFN only[4-6]. Furthermore, a meta-analysis of 12 comparative studies of Peg-IFN α-2a and α-2b[7] showed a higher rate of sustained virological response (SVR) with Peg-IFN α-2a compared to α-2b. Nevertheless, current guidelines [8-9] recommend the use of either types of peg-IFN in combination with RBV for the treatment of choice.

NEW ANTIVIRAL DRUGS

It is very well known that antiviral treatment based on the combination of Peg-IFN and RBV has many limitations. Firstly, the efficacy of treatment highly depends on factors related not only to patients, but also to virus or treatment. The presence of co-infection with HIV, frequent in the prison setting, conditions lower rates of SVR, as confirmed by many studies[11,12]. Similarly, the use of Peg-IFN based therapy is contraindicated for certain clinical conditions (major depressive disorder, decompensated cirrhosis, etc.) thus hepatitis C treatment is limited with these patients. On the other hand, other factors related to the patient, such as advanced age, being male or a black person are associated with lower rates of SVR[13,14]. HCV genotype plays an important role in achieving SVR to treatment. SVR rates in patients infected with genotypes 1 or 4 are about 50%, in comparison with 85% in carriers of genotypes 2 or 3[7]. Other viral factors, such as a viral load higher than $6x10^5$ Ul/mL, are also associated with a poorer response to treatment with Peg-IFN and RBV[6]. Finally, certain factors related to treatment play an important role in achieving SVR. In particular, the use of RBV doses higher than 10.6 mg/kg was associated with a higher rate of SVR[15].

Given these limitations, developing new antiviral drugs and strategic ways which could achieve higher cure rates in chronic hepatitis C together with less adverse effects must be a priority. Besides, they must be applicable in patients with decompensated cirrhosis.

NS3/4ª SERINE PROTEASE INHIBITORS

HCV genome is a single strand of RNA of about 10,000 nucleotides in length. During the transcription of viral RNA, a polyprotein of about 3,300 amino acids is obtained, from which structural and non-structural proteins are released. The amino-terminal domain of NS3 protein forms together with the co-factor NS4A a serine protease which is responsible for the cleavage of the HCV polyprotein into 4 non-structural functional proteins. What is important in the replication cycle of HCV NS3/4A serine protease is that viral replication cannot start until all proteins have been cleaved from the initial polyprotein.

So far there have been two main classes of inhibitors of serine protease NS3/4A of genotype 1 HCV, covalent inhibitors like Telaprevir and Boceprevir, derived from the a-ketoamides; and non-covalent linear inhibitors, not only those which contain carboxylic acid (eg. BI-1335) but also those derived from the sulfones (eg. BMS-650032, danoprevir and vaniprevir).

TELAPREVIR

It is a peptidomimetic inhibitor of NS3/4A serine protease that binds covalently but reversibly to HCV protease with a slow pattern of binding and dissociation[16]. Telaprevir has shown efficacy in phase II of PROVE-1[17] study, in which a regimen based on the combination of Telaprevir for 12 weeks together with PegIFN and RBV for 12, 24 and 48 weeks, and a standard regimen PegIFN and RBV for 48 weeks were compared. The SVR was significantly higher in Telaprevir groups (61-67 %) compared to standard treatment (41%). Similarly, PROVE-3 study assessed the efficacy of Telaprevir in previous non-responders to interferon therapy, showing significantly higher SVR rates compared to standard treatment (51-53% vs 14 %, respectively). The most common adverse effects of treatment with Telaprevir included: exanthema, anaemia and gastrointestinal symptoms, resulting in withdrawal of treatment in 18% of patients compared to 4% in the standard treatment group. In terms of resistance, 7% of patients treated with Telaprevir selected resistant HCV Telaprevir strains, in particular, patients infected with subtype 1a.

Protease Inhibitors	Polymerase inhibitors		NS5A inhibitors
	Nucleoside analogues	Non-nucleoside analogues	
• Telaprevir • Boceprevir • Danoprevir • Vaniprevir • BI-1335 • TMC-435 • GS-9256	• RG-7128 • PSI-7851	• GS-9190 • Filibuvir • BI-7127 • ANA-598 • VX-222 • VCH-759	• BMS-790052

Table I. New antiviral drugs in the most advanced stage of development.

Protease Inhibitors	Nucleoside analogues	Non-nucleoside analogues
• Interaction with catalytic triad • Genotype-dependent activity • High-level resistance	• Natural substrate analogues • Phosphorylation need • Chain terminators • Activity against different genotypes • High genetic barrier	• Allosteric inhibition • Genotype-dependent activity • High-level resistance • Influenceable by polymorphisms

Table II. Principal characteristics of the new classes of antiviral drugs.

Phase III of ADVANCE[19] and ILLUMINATE[20] studies have shown the superiority of triple therapy with Telaprevir, PegIFN and RBV over treatment with PegIFN and RBV, showing significantly higher SVR rates. Approval of Telaprevir in Spain is expected in late 2011.

BOCEPREVIR

It is a linear covalent inhibitor of serine protease. Phase II of SPRINT-1[21] study has shown the superiority of triple therapy based on Boceprevir + PegIFN + RBV over standard treatment, with significantly higher SRV rates (54-75% vs 38%). These findings have been confirmed in phase III of SPRINT-2[22] trials, in PegIFN naïve-patients infected with genotype 1 and in RESPOND-2[23] study, in previous non-responders to standard treatment. In these studies, treatment with Boceprevir was associated with anaemia and gastrointestinal symptoms, resulting in withdrawal of treatment in up to 15% of patients.

Telaprevir is administred twice daily for 12 weeks, while Boceprevir is administred throughout treatment (24-48 weeks) three times daily. Length of treatment (24-48 weeks) will adapt to the presence of virological response at weeks 4 to 12. As in the case of Telaprevir, approval of Boceprevir in Spain is expected in late 2011.

OTHER NS3/4A INHIBITORS

Other protease inhibitors of HCV are at different stages of development. Danoprevir is non-covalent macrocyclic inhibitor, which has also demonstrated activity against genotype 2 and 3 HCV[24]. Results at week 12 in phase II of ATLAS[25] trial have shown the superiority of triple therapy with Danoprovir, PegIFN and RBV over standard treatment. Given its pharmacokinetics and metabolism of the liver by cytochrome P450, treatment with Danoprevir will require boosting with Ritonavir[26]. Other drugs in this family such as BI-1335, TMC-435 or Vaniprevir are in different stages of development, showing promising results in clinical trials so far.

NS5B RNA POLYMERASE INHIBITORS

HCV NS5B polymerase is an RNA-dependent polymerase that plays a critical role in viral replication. Thus, inhibitors which have this enzyme as specific target have been developed. At present,

there are two different families of polymerase inhibitors, the nucleoside analogues and non-nucleoside analogues. It is important to point out that inhibitors of nucleoside polymerase are the only antiviral against HCV that are active against all viral genotypes.

NUCLEOSIDE POLYMERASE INHIBITORS

The RG-7128 is a prodrug of PSI-6130, a cytidine analogue that is currently in phase II clinical trials. In previous trials, this drug has shown a high specificity for HCV, with minimal cellular toxicity and effect on mitochondrial DNA, unlike what happens with many nucleoside analogues used in the treatment of HIV. This drug acts as a chain terminator after experiencing triphosphorylate intracellular, preventing elongation of the nascent viral RNA chain.

Preliminary results of phase IIb PROPEL[27] on 408 patients infected with genotypes 1 or 4 showed the superiority of a regimen based on the combination of RG-7128 and PegIFNa + RBV for 8 – 12 weeks followed by PegIFNa and RBV until 24 or 48 weeks of treatment have been completed. The rate of rapid virological response (RVR) was 62 % in the triple therapy group compared to 18% in the standard treatment group. At 12 weeks of study, 80-87 % of patients with triple therapy had undetectable viral load, compared to 49% in the control group.

The INFORM-1[28] study evaluated the efficacy of a treatment regimen without PegIFN in patients infected with genotype 1. The efficacy of a combination of two oral drugs, the RG-7128 (nucleoside analogue) and the RG-7227 (Protease Inhibitor) was examined. After 14 days of treatment, a mean decrease in HCV viral load of 5.1 $\log^{10}$ could be seen. The results of this study show for the first time that regimens without PegIFN could be effective in the treatment of chronic hepatitis C.

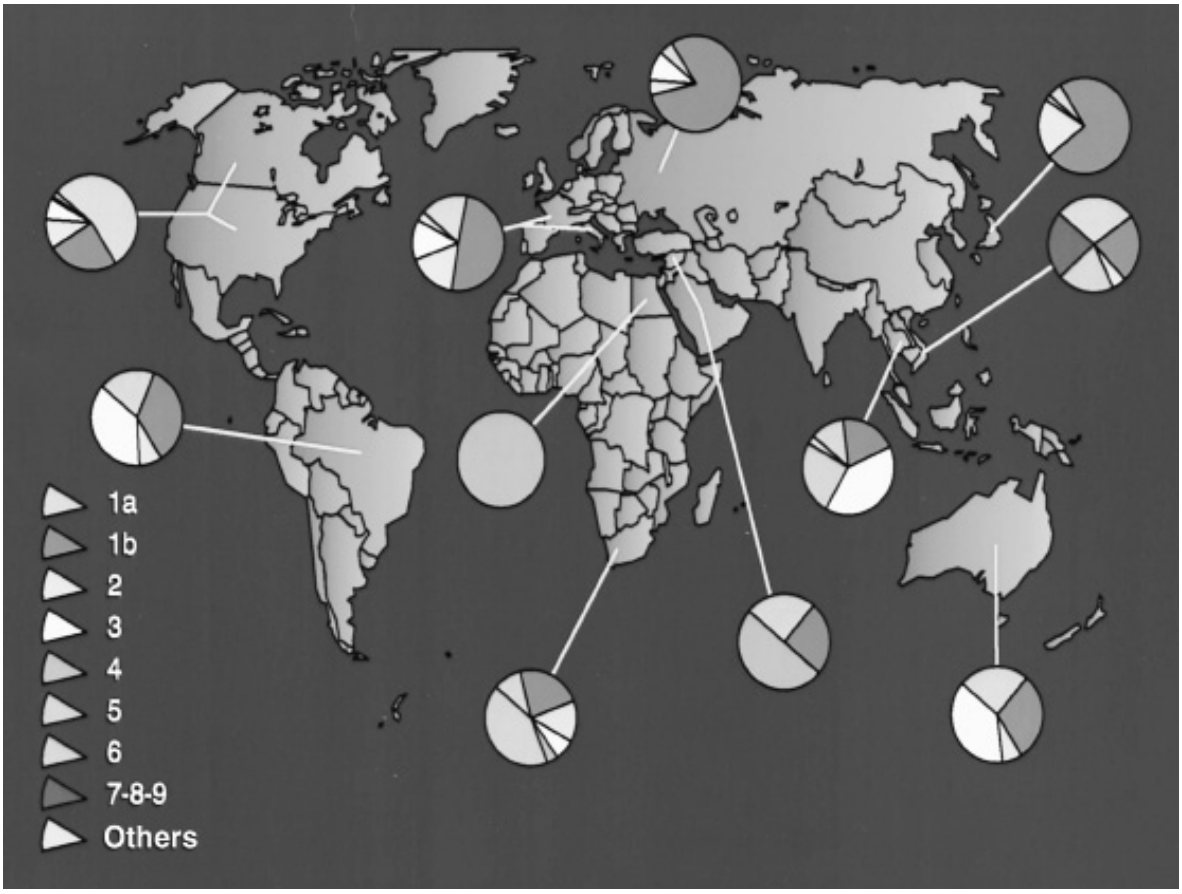

Figure 1. Worldwide distribution of HCV genotypes.

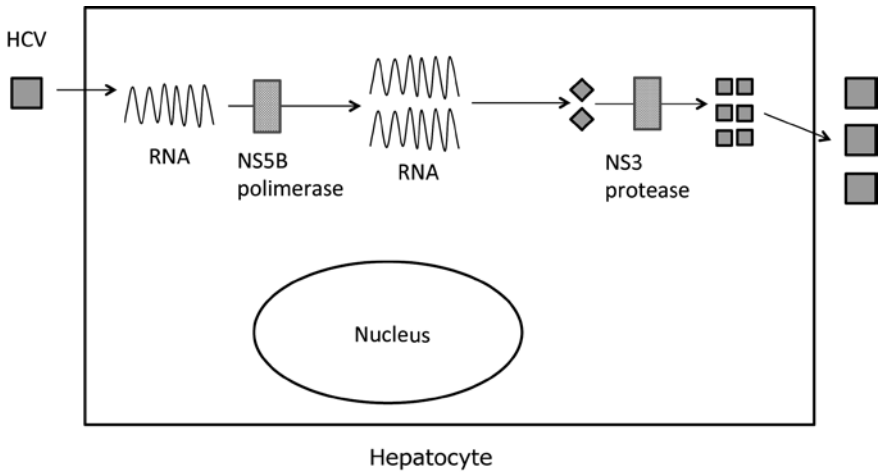

Figure 2. HCV life cycle.

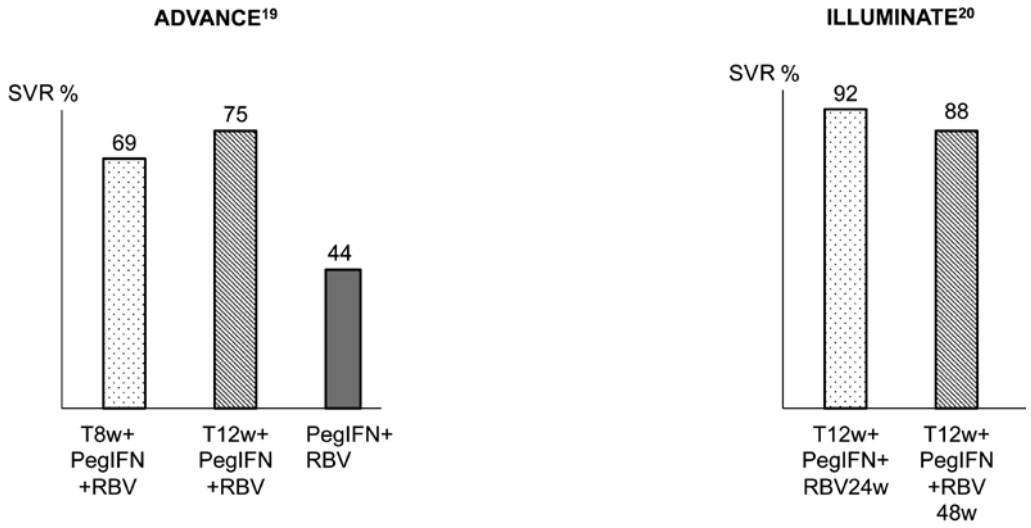

Figure 3. Results from Phase III trials with Telaprevir based therapy in patients who were new to treatment.

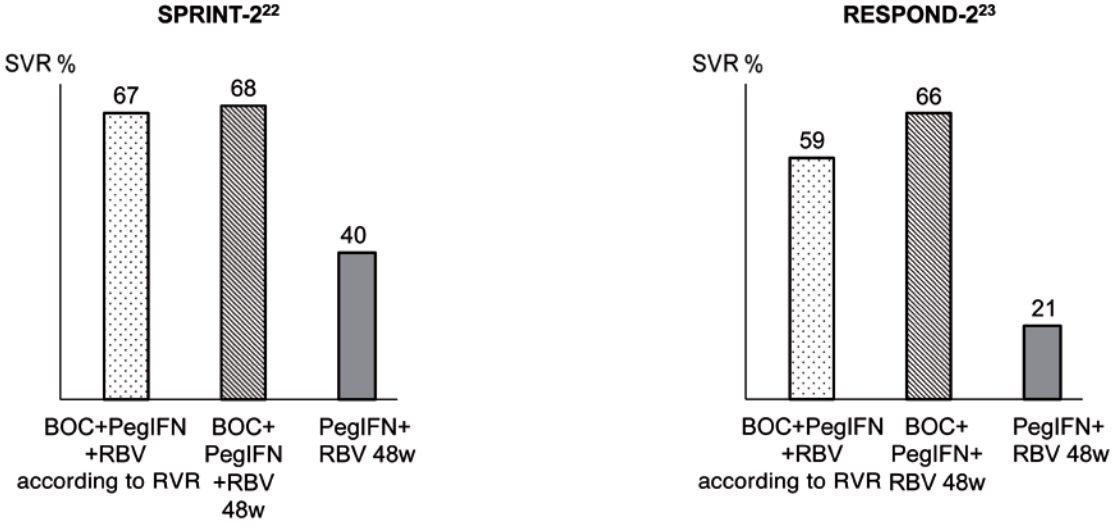

Figure 4. Results from Phase III trials with Boceprevir based therapy.

Finally, it is important to point out that the studies carried out so far have not identified resistance in patients treated with RG-7128, which could indicate a higher genetic barrier than that observed for protease inhibitors or non-nucleoside polymerase inhibitors. Similarly, the safety profile of RG-7128 appears to be very favourable, being headache and dry mouth the most significant adverse effects.

NON-NUCLEOSIDE POLYMERASE INHIBITORS

While nucleoside analogues act as chain terminator, non-nucleoside analogues polymerase inhibitors interact with polymerase outside the catalytic centre, producing allosteric changes in the enzyme which critically affect their function. Since there are different binding sites to the polymerase, cross-resistance within drugs of this class is limited and could allow combination of several of them.

Different drugs of this family are at different stages of development. Filibuvir is a highly selective inhibitor of high potency, which has shown efficacy in a phase II trial with PegIFN and RBV. The selection of the mutation M4231 / V in the polymerase significantly decreases its activity. GS-9190 is a imidazopyridine derivative, which has shown efficacy in phase I trials, showing a pattern of dose-dependent inhibition[30]. Other drugs, such as ANA-598, are being evaluated in phase II[31] studies, while HCV-759 or BI-7127 are in earlier stages of development[32,33].

THE FUTURE OF CHRONIC HEPATITIS C TREATMENT

The emergence of new antiviral drugs for the treatment of chronic hepatitis C is an important step forward in order to improve the response to treatment of this disease and to provide solutions to the many patients who are either non-responders to current treatment or not candidates for PegIFN and RBV. The evidence available so far underlines the high efficacy of protease inhibitors, and the high genetic barrier and effectiveness against different genotypes of nucleoside polymerase inhibitors. Nevertheless, there are some doubts regarding some aspects related to new treatments for HCV. Firstly, it seems that, at least at first, PegIFN and RBV are likely to be used together with most of these new drugs. This could keep on punishing and restricting the benefit of the new medication. The INFORM-1[28] study is assessing the efficacy of a regimen without interferon, based on the combination of a protease inhibitor and a polymerase inhibitor. Although results so far are encouraging, the development of therapeutic regimens without interferon suitable for a broad spectrum of patients may be delayed in time.

The emergence of resistance to antivirals is another important limitation of these new drugs[35]. Resistance to protease inhibitors may confer cross-resistance to other drugs of the same family, complicating the rescue of the subgroup of non-responders. It is also important to clarify the persistence of mutations over time, although some data suggest that the majority of resistant mutant virus disappears within two years[36].

We must also take into consideration that most of the new antivirals against HCV have been designed to be used in patients infected with genotype 1, therefore their efficacy against other genotypes must be clarified. Significant genetic differences between genotypes 1 and 3 explain that the activity of protease inhibitors and that the potency of non-nucleoside polymerase inhibitors is either low or inexistent against genotype 3[37]. Activity against genotypes 2 and 4 can be identified, although it is usually very low. Finally, the role that specific therapies can play in the treatment of special patient groups, such as those co-infected with HIV, decompensated cirrhosis or those who are non-responders or relapsers to PegIFN and RBV treatment has to be determined.

CONCLUSIONS

The development of new drugs that are active against HVC opens up new possibilities for the treatment of this disease. These antiviral drugs may lead to better rates of cure with shorter duration of treatment. For the time being, the toxicity and development of resistance are the most important limitations of these drugs. Although, they will be administered together with PegIFN and/or RBV at first, they are expected later on to be used in combinations without them. Without a doubt, a revolution in the treatment of hepatitis C has started.

CORRESPONDENCE

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