Hepatitis C associated with substance abuse: ever closer to a treatment without Interferon

Hepatitis C asociada al abuso de sustancias: nunca tan cerca de un tratamiento sin Interferón

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Abstract

With 3-4 million of new infections occurring annually, hepatitis C virus (HCV) infection is a global Public Health problem. In fact, hepatitis C virus infection is one of the leading causes of liver disease in the world; in Western countries, two thirds of the new HCV infections are associated with injection drug use.

The treatment of hepatitis C will change in the coming years with the irruption of new anti-HCV drugs, the so called Direct Antiviral Agents (DAA) that attack key proteins of the HCV life cycle. The new antiviral drugs are effective, safer and better tolerated. The 2014 WHO HCV treatment guidelines include some of them. The new DAA are used in combination and it is expected that Interferon will be not necessary in future treatment regimens against HCV infection.

The irruption of new and potent antivirals mandate the review of the current standards of care in the HCV infected population. More inclusive and proactive treatment policies will be necessary in those individuals with substance use disorders.

Key words: substance abuse; hepatitis C; treatment; direct antiviral action.

Resumen

La infección por el virus de la hepatitis C (VHC) es un problema de Salud Pública de primera magnitud; cada año ocurren entre 3 y 4 millones de nuevas infecciones y de hecho, la hepatitis crónica C es una de las principales causas de enfermedad hepática en el mundo. Usar drogas por vía parenteral está en el origen de dos de cada tres nuevas infecciones por VHC en el mundo occidental.

El tratamiento de la hepatitis C va a cambiar en los próximos años. El cambio es debido a la aparición de los llamados Antivirales de Acción Directa (AAD), unos fármacos que actúan contra proteínas clave del ciclo vital del VHC y que serán más eficaces, mejor tolerados y se administrarán durante menos tiempo. En este sentido, la nueva guía de tratamiento de la OMS en 2014 ya incluye alguno de ellos en sus recomendaciones; los nuevos fármacos se utilizarán en combinación y probablemente se podrá prescindir del Interferón.

Con la aparición de más y mejores antivirales contra el VHC es probable que debamos revisar el modelo asistencial vigente y orientarlo hacia uno más ágil e integrador, que trate al mayor número posible de pacientes, incluyendo a aquellos con abuso de sustancias.

Palabras clave: abuso de sustancias; hepatitis C; tratamiento; antivirales acción directa.

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Treatment of chronic hepatitis C will change in the coming years. This change will occur due to the introduction of medication that is more efficacious, better tolerated, that scarcely generates any pharmacological resistance, and that is administered during shorter periods of time. Studies published since 2012 have revealed the efficacy of some of these drugs, and if this is indeed the case, it indicates the need to expand such treatment to a larger numbers of patients; detection of the infection and assessment of liver disease will be relevant if it is confirmed that infection cure can reach levels greater than 90%, regardless of viral genotype or of previous treatment failure. When the efficacy of the new therapies is confirmed in clinical trials, treatment of the illness will be generalized, and subsequently the population effectiveness of those therapies will be demonstrated. But clinical efficacy and population effectiveness are not the same thing; the latter is necessary to reduce the enormous burden of hepatitis C virus (HCV) on society. What has all this got to do with substance users? A great deal. In Western countries, two out of three new HCV infections occur in individuals who have injected or are injecting drugs, but this population – not by coincidence – receives the least treatment for HCV. The reasons why people with a history of substance abuse do not receive HCV treatment are quite diverse, and are described in this review, but one of the most widely cited is their poor tolerance to Interferon, an immunomodulatory drug that has formed part of the core of HCV treatment for some two decades. But if the advantages of the new medications are confirmed, patients with substance-use-related HCV will be more likely to seek treatment, as occurred after the irruption of the highly effective antiretroviral drugs for the treatment of human immunodeficiency virus (HIV).

Epidemiology of hepatitis C

HCV infection is one of the principal causes of liver disease worldwide (Shepard, Finelli, & Alter, 2005). Prevalence of the infection in the world population, disregarding marked regional differences, is close to 3% – equivalent to some 185 million people. It is estimated that 10 million individuals infected by HCV are, or have been, injection drug users (IDUs) (Nelson et al., 2011; Mohd Hanafiah, Groeger, Flaxman, & Wiersma, 2013).

Globally, prevalence of the infection is higher in men, in people aged 30 to 49, and in those with low socio-economic status (Alter, 2007). Risk factors for infection vary, but transfusions (blood and/or blood derivatives) carried out before 1992, the use of re-usable healthcare materials and injection drug use are still the most important ones (Des Jarlais et al., 2003; Memon & Memon, 2002). In the USA there are over 2 million injection drug users, and the incidence of HCV infection is estimated at between 8% and 25% annually among the youngest of these. Data from the US also indicate that 30,000 new cases of infection are diagnosed each year, and that the incidence of infection is greater in new drug users and during the first year of drug use (Nelson et al., 2011; Page et al., 2009). It has been demonstrated that the transmission of HCV is 10 to 15 times higher than that of HIV (Page et al., 2009; Page, Morris, Hahn, Maher, & Prins, 2013), which reveals just how easily it can be transmitted in this population.

Also, people with alcohol use disorder present higher prevalence of HCV infection than the general population. Up to 20% of a series of 700 patients who sought treatment for alcoholism in the Barcelona were infected with HCV, according to a recent study (Rivas et al., 2013).

HCV is the principal cause of liver transplant and of hepatocellular carcinoma (HCC) in Western countries (Freeman et al., 2008; Yang et al., 2011). In fact, HCC and cirrhosis of the liver have increased in recent years among people infected with HCV, and it is forecasted that incidence of the two diseases will increase significantly in the coming decades (Mehta et al., 2010; Rein et al., 2011). A study in the US highlighted the growing number of deaths among those infected with HCV, which is now higher than that for deaths attributed to HIV/AIDS (Ly et al., 2012); the same study indicated that deaths related to HCV occur mainly in the age group 45 to 64 (Ly et al., 2012), and this has led health authorities in the US to recommend that the general population in this age group should be screened for HCV. It has been estimated, moreover, that a million people with HCV infection in the US will die as a result of complications related to the illness if they go untreated (Rein et al., 2011, 2012).

In Spain, estimates reveal that the number of people with HCV infection is around 430,000, with people older than 50 showing the highest prevalence of infection. The explanation for this can probably be found in the explosion of intravenous heroin use that occurred among young people in this country from the early 1980s onwards (Cornberg et al., 2011).

Natural history of hepatitis C

HCV causes an acute infection that remains asymptomatic in the majority of cases. Around 20-25% of substance-abusing patients will eliminate the viremia spontaneously in the 6 months following infection (Grebely et al., 2012; Page et al., 2009). Among the factors associated with spontaneous cure of the infection are being a woman, infection through genotype 1 (the most common in our context), and being a homozygote for the Interleukin-28 (IL-28B) gene, a gene that codes the Interleukin-23 protein, involved in the replication of HCV (Liu, Fisher, Thomas, Cox, & Ray, 2012; Page et al., 2009). On the other hand, 75-80% of those infected will develop a chronic infection, and the risk of developing cirrhosis, HCC, or other extra-hepatic complications may be

relatively high in the medium and long term (Grebely, de-Vlaming, Duncan, Viljoen, & Conway, 2008), especially if we take into account that the majority of patients with a history of substance abuse become infected at a very early age.

In chronic HCV infection, hepatic histological alteration is characterized by portal and lobular necro-inflammation. In a third of patients, the infection will follow an indolent course, but in the rest there will be a progressive increase of hepatic fibrosis, which will manifest clinically on the long term (Afdhal, 2004). The progression of hepatic fibrosis is not a linear process, since factors such as HIV infection, HBV, alcohol use and others can accelerate it (Muga et al., 2012; Cartón et al., 2011); age at the time of infection, male sex, obesity, diabetes mellitus and hepatic steatosis have also been associated with greater risk of fibrosis progression (Afdhal, 2004; Poynard, Bedossa, & Opolon, 1997). Once established the final phase of the disease, or liver cirrhosis, the probability of presenting a decompensation is 5% the first year and 30% ten years after diagnosis, whilst the risk of occurrence of HCC is 1-4% per year (Dore, Freeman, Law, & Kaldor, 2003; Raimondi, Bruno, Mondelli, & Maisonneuve, 2009). In general, it is accepted that median survival of patients presenting a first decompensation of liver cirrhosis is 5 years (Dore et al., 2003).

Diagnosis and assessment

Hepatic fibrosis is the principal marker of the course of liver disease (Thomas & Seeff, 2005). Liver biopsy has been considered the most reliable method for assessing the presence of fibrosis, and hence the most suitable tool for selecting candidates for treatment. However, recent years have seen the introduction of new methods for assessing fibrosis levels without the need for an invasive procedure, with elastography and biochemical markers playing an increasingly important role (de Ledinghen et al., 2006; Sanvisens et al., 2009; Sterling et al., 2006; Wai et al., 2003).

Among the biochemical markers, the APRI (AST-to-Platelet Ratio Index) or the FIB-4 (age, platelets, AST, ALT) are easy to use, since their calculation requires parameters that are employed in the routine clinical assessment of patients with liver disease. These two indexes are recommended by the World Health Organization (WHO) in the recently-published Guidelines for the screening, care and treatment of persons with HCV (World Health Organization, 2014); moreover, they have been validated in patients with HCV infection (Mallet et al., 2009; Vallet-Pichard et al., 2007; Wong et al., 2010), though their validity in chronic alcohol users might be limited.

Knowing the magnitude of hepatic damage in this group of patients with chronic hepatitis C is of crucial importance with the advent of new therapeutic regimens. In our experience, the prevalence of moderate and severe hepatic fibrosis is 40% and 17%, respectively, in this population (Sanvisens et al., 2011).

Current situation of hepatitis C treatment in substance-abusing patients

The prevalence of HCV infection in injection drug users is very high (50%-80%), and the most common genotypes are 1a, 1b and 3 (Robaeys et al., 2013). Despite the fact of being the population at greatest risk of infection, these patients tend not to receive treatment for chronic hepatitis C. According to European Union figures, the number of patients treated for hepatitis C does not reach 0.5% of the 700,000 people currently receiving methadone treatment (European Monitoring Centre for Drugs and Drug Addiction 2011).

In general, current standard treatment for hepatitis C is received over a period of 24 to 48 weeks, and the drugs employed are pegylated Interferon (PEG-IFN), Ribavirin (RBV) and Boceprevir or Telaprevir, these last two as first-generation protease inhibitors (World Health Organization, 2014). Treatment with PEG-IFN consists in the administration of weekly subcutaneous injections, and the side-effects are well-known and include flu-like symptoms, anxiety, depression, asthenia and cytopenias which, if they affect the erythrocyte series, may require treatment with erythropoietin (Chung, 2012). The ultimate goal of hepatitis C treatment is the eradication of the virus; the so-called sustained viral response (SVR) defined as undetectable HCV RNA 6 months after the end of treatment. Given its adverse effects, mainly on the Central Nervous System, a portion of patients receiving PEG-IFN should add antidepressants to their hepatitis C treatment.

In patients with a history of substance abuse, the healthcare reality of hepatitis C treatment is that only a minority are treated (Grebely et al., 2008; Mehta et al., 2008); the reasons for not receiving treatment are many, but three of them stand out: risk of poor therapeutic compliance, risk of reinfection and risk of exacerbation of psychiatric comorbidity (Edlin, 2002; Kramer et al., 2011).

At the care level there are still other barriers to access treatment for chronic hepatitis C, such as the lack of care contexts for the treatment of this population or the insufficient clinical training in the management of liver disease and substance abuse (Grebely & Tyndall, 2011; Litwin et al., 2007; Reimer & Haasen, 2009). Here in Spain, although the rate of diagnostic screening is high, the assessment of substance abuse and of medical and psychiatric comorbidity is somewhat heterogeneous, and involves various specialities; moreover, the care protocols for the assessment of drug dependence, psychopathology and liver disease are long-winded, and certainly do not favour the retention of these patients in the health system. Lack of knowledge about the illness by patients themselves and lack of social support have also been cited as barriers to acceding to treatment (Alavi et al., 2013). Table 1 includes a summary of the principal barriers to access to HCV treatment.

Various studies indicate that alcohol or substance use does not usually affect adherence to hepatitis C treatment,

Table 1.
Major difficulties in access to treatment of chronic hepatitis C in patients with substance abuse

In the health system	In patients
Insufficient knowledge of hepatitis C: – Limited training – Inexperience in the evaluation of liver damage – Low awareness of the need for treatment: • asymptomatic disease • Ignorance of the stage of fibrosis • Other priority co-morbidities	Inadequate knowledge of hepatitis C: – Limited Education in relation to HCV
Misperceptions about treatment: – High risk / benefit – Patients with substance abuse are poor candidates: • Addiction / psychiatric illness • Poor adherence	Low perceived need for treatment: – Asymptomatic disease – Ignorance of the stage of fibrosis – Other priority co-morbidities
Lost entries or delayed entries in the care circuit for hepatitis C	Misperceptions about treatment: – High risk / benefit – Fear of the complexity of treatment and side effects
	Poor retention in care circuits: – Addiction / psychiatric illness – Inadequate access to care circuits – Stigma / poorer social conditions

and nor does such abuse imply poorer response rates, even if more difficulties for treatment completion have been observed (Anand et al., 2006; Grebely & Tyndall, 2011; Hellard, Sacks-Davis, & Gold, 2009). A recent systematic review on drug users eligible for HCV treatment with PEG-IFN and RBV yielded a global SVR of 56% (37% for genotypes 1/4 and 67% for 2/3) (Aspinall et al., 2013); these figures are somewhat lower than those reported in most clinical trials for these drugs, but are similar to those described in two studies on the effectiveness of the treatment (39%-46% for genotype 1 and 70%-84% for genotype 2/3) (Borroni et al., 2008; Innes et al., 2012). In that same systematic review (Aspinall et al., 2013) a high level of treatment adherence was observed, 83%, somewhat higher than that shown in patients not abusing substances (McHutchison et al., 2002; Ravi, Nasiri Toosi, Karimzadeh, Ahadi-Barzoki, & Khalili, 2013) – though it should be borne in mind that the differences observed would be explained by the way adherence is defined. Moreover, the HCV reinfection rate was moderate (2.4 per 100 person-years), suggesting that this has little effect on long-term treatment effectiveness (Aspinall et al., 2013).

Paradigm shift: new treatments for hepatitis C without IFN

The growing numbers of patients that will need hepatitis C treatment, the contraindications and side effects of current treatment with IFN, and improved knowledge of the HCV life cycle have led to the development of new drugs. The advent of treatment regimens without IFN will represent a fundamental step forward in increasing treatment access. Everything points to the fact that patients with a history of substance abuse and hepatitis C will be no exception.

This paradigm shift in the treatment of hepatitis C begins to become a reality after the approval in the USA of the second-generation protease inhibitors and of the first HCV polymerase inhibitor in 2013. The first step in the direction of new treatment came after 2011, with the introduction of first-generation HCV protease inhibitors (Telaprevir and Boceprevir).

Second-generation protease inhibitors provide a better barrier with regard to pharmacological resistance, have fewer adverse effects, and show enhanced pharmacological activity against other HCV genotypes (Wendt et al., 2014). Protease and polymerase are key proteins in the HCV life cycle, only understood in detail in the last few years. Various pharmaceutical companies have analyzed therapeutic targets in key areas of the virus. The identification of these new therapeutic targets, based on attacking non-structural proteins of the virus, has led to the recognition of more than 10 Direct Antiviral Agents (DAAs). These agents include inhibitors of the protease NS3/4A, inhibitors of the polymerase NS5B, inhibitors of the NS5A complex, inhibitors of cyclophilin and direct inhibitors of RNA viral polymerase. Antivirals against HCV and Sofosbuvir (Lawitz & Gane, 2013) or Simeprevir (Asselah & Marcellin, 2014) approved by the FDA at the end of 2013, and others such as Daclatasvir (Gentile et al., 2013), Asunaprevir (Suzuki et al., 2013), Faldaprevir, Deleobuvir (Zeuzem et al., 2013) or Ledipasvir (Link et al., 2014), are highly efficacious, and set out to eradicate the virus through oral therapeutic regimens of 12 weeks in some genotypes, and with few adverse effects (Gane et al., 2014; Sulkowski et al., 2014). In this regard, the recent Guide published by the WHO in April 2014 already includes in its recommendations the two drugs approved by the FDA (sofosbuvir, simeprevir) and recently incorporated into the Spanish National Health System, and anticipates regular updates as new licences are granted (World Health Organization, 2014). Even though clinical trials on the new drugs have not been carried out on substance-injecting patients, the WHO Guide recommends not excluding this population from treatment (priority recommendation); likewise, the WHO recommends detecting heavy drinkers and offering such patients interventions for reducing their intake.

We should point out the need for studies that analyze potential pharmacological interactions between DAAs and

the drugs most widely used in the treatment of substance abuse. Simeprevir and faldaprevir are metabolized by the cytochrome P450 system, and it is possible that they show pharmacokinetic interactions with drugs such as methadone and buprenorphine (Mauss & Klinker, 2013).

In any case, improvements in the pharmacological treatment of hepatitis C should perhaps be accompanied by changes in the clinical care model applied to substance-abusing patients; diagnosis of the infection and clinical assessment are of great importance in the prioritization of treatment for the most in need. Health care professionals involved in the treatment of substance abuse should play a key role in ensuring that these patients are clinically evaluated, are treated for their illness, and obtain therapeutic results similar to those we would expect to obtain in patients without substance abuse. Establishing a more inclusive care model for patients with substance-use-related hepatitis C will become necessary in the face of all the imminent changes.

Conclusion

The substantial burden of liver disease and the high incidence of HCV infection in substance-abusing patients make it necessary to improve diagnosis and treatment in this population. New, innovative drugs are appearing that directly attack proteins responsible for forming the viral replication complex of HCV; the combination of two or more of these drugs can be highly efficacious against the majority of HCV genotypes and in the majority of clinical situations, including liver cirrhosis. With the introduction of such efficacious and well-tolerated drugs, there is a need to review the current care model and replace it with a more flexible and integrated one that attempts to treat the highest possible number of HCV-infected patients. Figure 1 shows a first approach to a multidisciplinary care model. Likewise, optimizing the prevention, diagnosis, assessment and treatment access of chronic hepatitis C is high-priority. The approaches that can be proposed are diverse, and would include:

- Identifying perceived barriers and needs in primary care and drug-dependence clinics and developing educational activities for improving knowledge about chronic hepatitis C,
- Reviewing the process of clinical assessment of patients with hepatitis C associated with substance abuse,
- Categorizing patients' clinical situation: new diagnosis, previously treated, stage of liver disease, etc.
- Identifying patients at risk of HCV infection and preventing infection through a brief intervention and screening for viral hepatitis.
- Offering treatment for alcohol or drug abuse to patients with chronic hepatitis C.

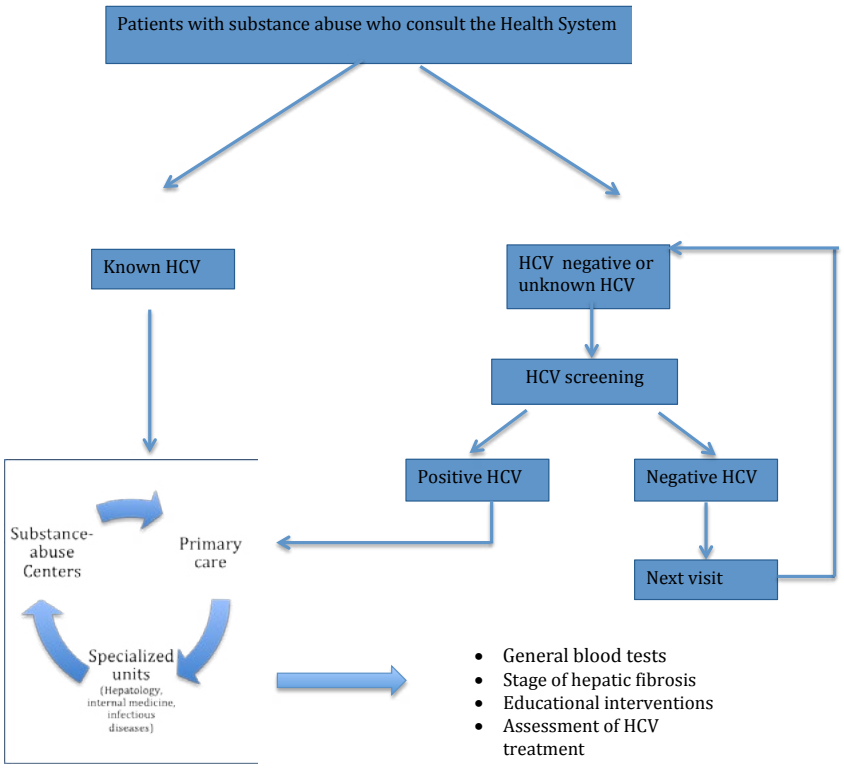

Figure 1. Model for increasing the participation of substance-abusing patients in access to treatment for chronic hepatitis C

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Conflicts of interests

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