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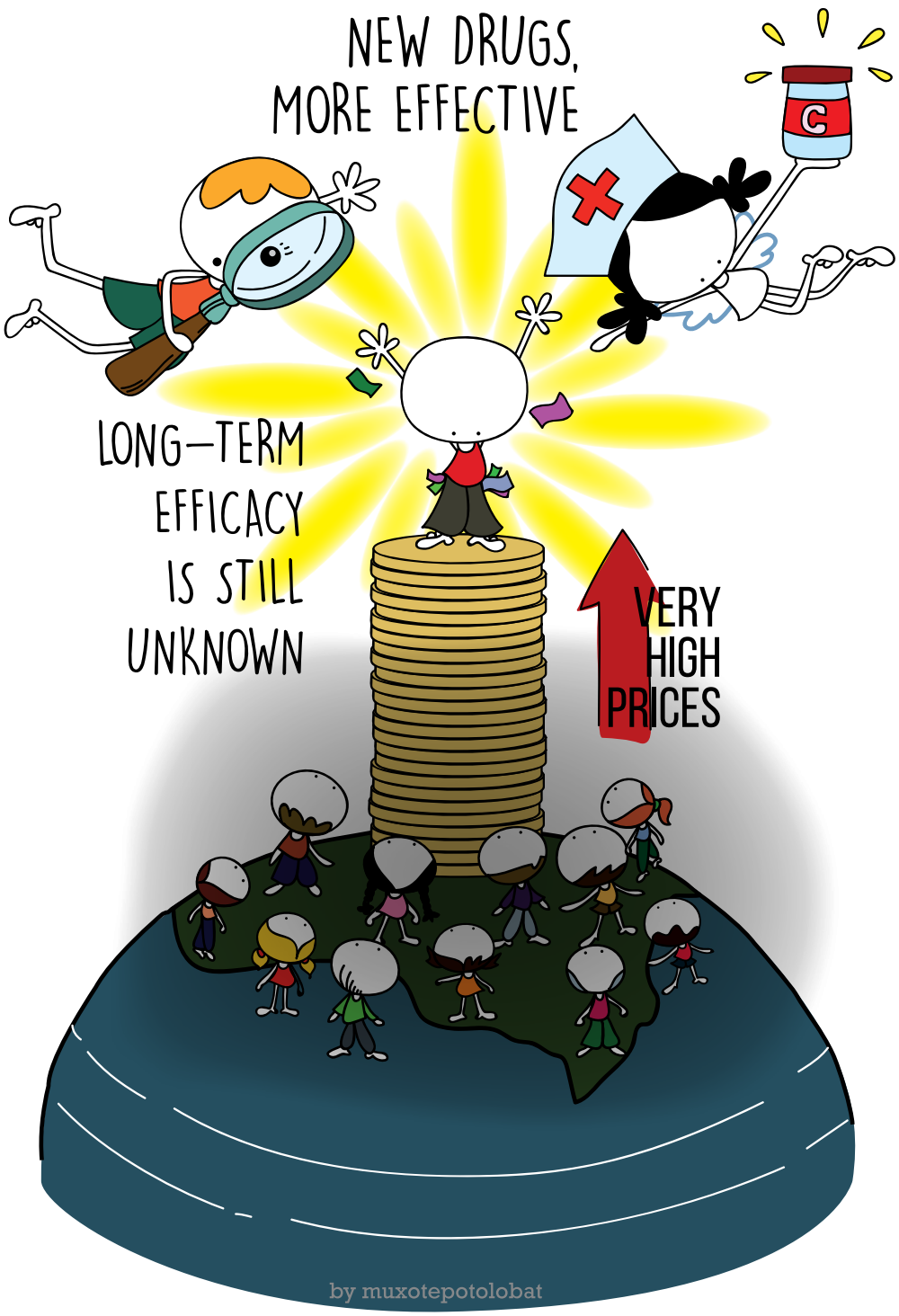
Management of hepatitis C, time for hope?



Objective: To review relevant aspects of hepatitis C (HCV) infection and propose an approach to disease management.
Methods: A review of the published scientific literature was carried out in PubMed and updated on 9 December 2015.
Results and conclusions: A management approach is proposed for HCV treatment. The situation is promising as newer drugs provide a clear improvement in efficacy. However, the clinical trial evidence has some limitations. These include a lack of head-to-head comparisons of efficacy among different new drugs in the same study population; potential differences in drug effects in actual practice compared with those observed in the trials; and a lack of knowledge of mid to long term treatment results or of the evolution of patients who are cured of the virus when fibrosis is already at an advanced stage. The exorbitant costs of these treatments greatly limit their use.
Key words: Hepatitis C, hepatitis C antiviral, hepatitis C virus.

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Introduction

Hepatitis C virus (HCV) infection is an important public health concern. Although in many countries epidemiological data are incomplete or estimates are based on poor quality data,[1] it is believed that worldwide more than 185 million people are infected.[2,3] Many of these people are unaware of their status and according to estimates only 24-35% of these patients are diagnosed with active infection.[4,5] In the western world HCV infection represents the most common cause of terminal liver disease and one of the main indications for liver transplantation.

There are large geographic differences in the presence of positive antibodies against HCV (seroprevalence), with countries classified as having high, intermediate or low prevalence. Spain is among the countries with an intermediate prevalence (1.5-3.5%), with large differences between urban and rural areas. The percentage of the population with positive viremia is approximately 1% (range 0.3%-1.8%).[5] In 2004, 106 new cases with positive antibodies against HCV were diagnosed in Navarre (some 640,000 inhabitants), 22% more than the year before. In 2014, age at diagnosis ranged from 30 to 84 (median 48), 40 (38%) women and 66 (62%) men.[6]

There are seven known genotypes with different subtypes. In Spain, genotype 1 is the most common, with a prevalence of 70% (4% subtype 1b and 26% subtype 1a). This is followed by genotype 3 (20%), genotype 4 (8%) and genotype 2 (3%),[7] with very few infections documented with genotypes 5, 6 or 7. While the genotype does not affect the evolution of chronic hepatitis, it does have a considerable impact on treatment choice and response.

Classically, treatment of chronic HCV infection has been based on the use of interferon alpha (IFN-α), a drug that modulates the immune response to the virus. It is administered subcutaneously, and has limited efficacy and numerous side effects. The approach to treatment has changed considerably over the last few years as a consequence of the development of direct-acting antiviral oral drugs that are very effective and have an acceptable safety profile.

The objective of this paper is to review the most relevant aspects of the HCV infection and present a proposal for disease management.

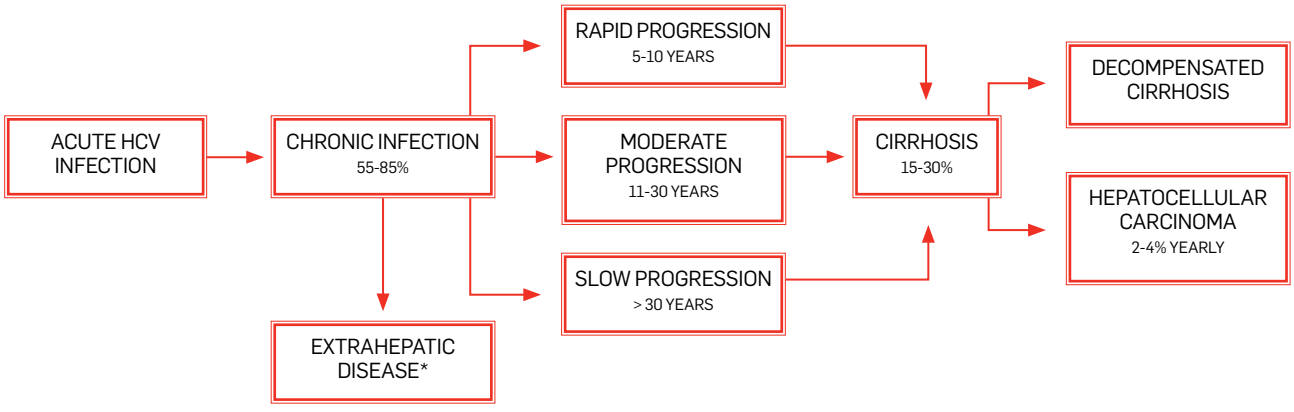
The natural history of hcv infection

An estimated 15-45% of infected individuals eliminate the HCV virus spontaneously within 6 months of infection with no need for treatment. The remaining 55-85% develop a chronic infection (>6 months), and of these, 15-30% develop liver cirrhosis within an average of 20 years (Figure 1).

In general, acute HCV infection is asymptomatic and, if the patient presents symptoms, these are mild and unspecific, which makes diagnosis difficult. Acute or sub-acute liver failure can occur exceptionally.

Chronic infection is diagnosed either when elevated liver transaminase levels are found in a routine analysis, or at a late stage when symptoms associated with chronic liver disease appear.

Figure 1. Natural history of HCV infection.



*Mixed Crioglobulinemia, membranoproliferative glomerulonephritis, thrombotic thrombocitopenic purpura, lichen planus, late cutaenous porphyria, and B-cell non-Hodgkin lymphoma. Source: Elaborated by "WHO2 Guidelines for the screening, care and treatment of persons with hepatitis C infection. April 2014."

Progression of HCV infection is influenced by various risk factors such as age at infection, the use of intravenous drugs, HBV and/or HIV co-infection, immunosuppression, obesity, steatosis, advanced age or genetic factors.[8]

Mechanisms of transmission

HCV infection is mainly parenteral. Transmission has been associated with:

- Injecting drugs of abuse, sharing needles.
- Blood transfusion and haemoderivatives and transplants of donor-infected organs (transfusions or transplants carried out before systematic screening for the virus was implemented, around 1990).
- Tatoos and piercings.
- Inadequate sterilization or reuse of medical material.
- Needlestick injuries (accidental pricks with needles from infected patients).

HCV can also be sexually transmitted or transmitted through inadvertent percutaneous exposure within families. Nevertheless, the risk of transmission through these routes is low. In heterosexuals, sexual transmission is mainly associated with the number of sexual partners. In recent years there has been an increase in infection rates in homosexual men. The risk of infection also increases in cases of HIV co-infection or intranasal drug use.

Perinatal transmission occurs in 5% of newborns of mothers with positive antibodies against HCV, and the risk is related to the mother's viremia levels at birth. For this reason, the risk of vertical transmission is greater when patients present HIV co-infection, because these patients usually present high HCV viral load. Transmission does not occur through breastfeeding.

However, in up to 44% of cases of re-infection, it is not possible to identify the risk factors for HCV within the previous 6 months.[9]

After a detailed clinical history is taken, patients who may have an HCV infection due to the presence of risk factors should undergo a blood test including a hemogram, coagulation and transaminase levels, HCV and other liver-related virus serology such as Hepatitis A, B and HIV.

Positive serology for HCV can indicate the presence of active infection (acute or chronic), a past infection or a false positive result,[10] the latter occurring among a higher proportion of tested patients in countries with a low prevalence of infection. For this reason patients with a positive serological result for HCV should undergo a PCR (Polymerase Chain Reaction) determination of viral DNA to detect viremia and also to classify the infection as active or not, which influences patient management. Cases of positive viremia should be referred to specialists to complete the evaluation and decide on the approach to management (Figure 2).

The genotype does not condition the evolution of hepatitis, but does affect the response to pharmacological treatment

The hepatologist should determine the genotype and subtype of the virus as these are needed when deciding on treatment. Likewise, specific characteristics of patients should be taken into account as they help determine the possible efficacy of some treatments. Through multivariate analysis, a variety of independent predictive factors of better response to treatment have been identified, namely:

Host-related factors: Young age, low body mass index, mild or moderate fibrosis, absence of mild steatosis and/or insulin resistance and Caucasian race.

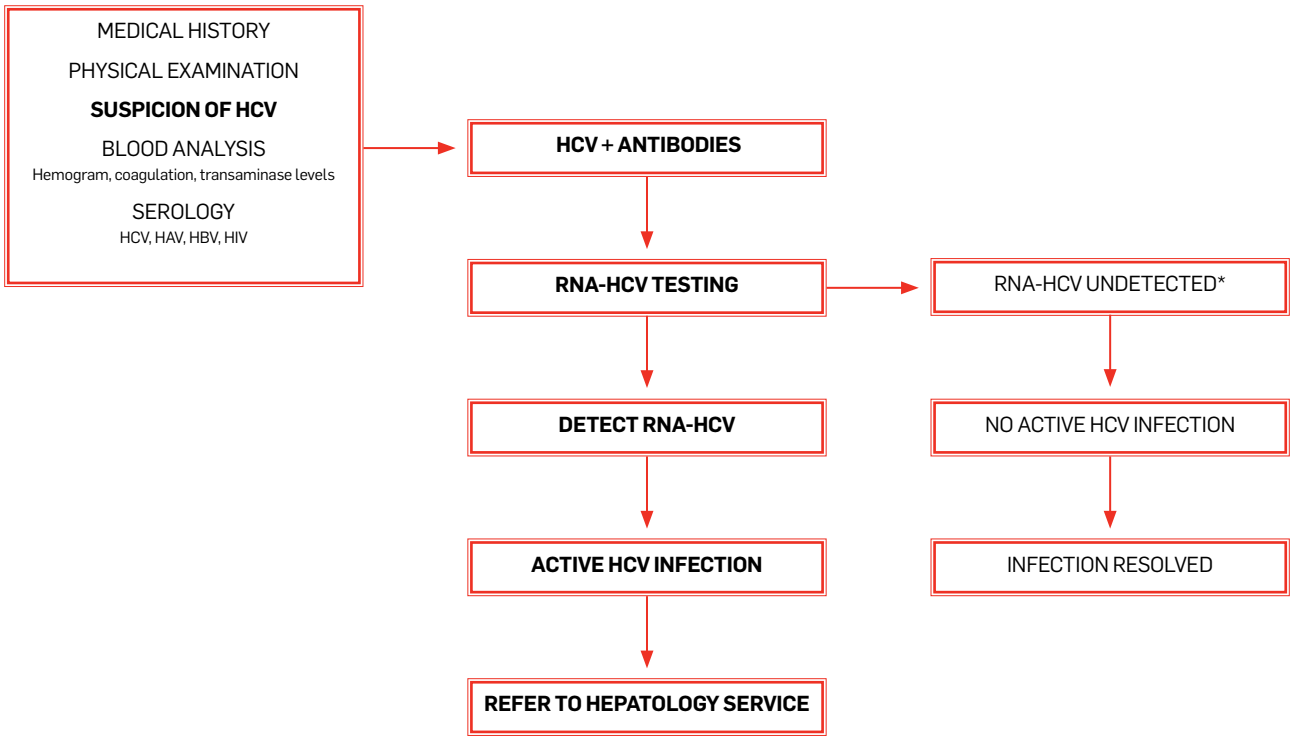
Virus-related factors: HCV genotypes other than 1 to 4 or low baseline viral load before treatment.[11,12,13]

In addition, the different polymorphisms of the interleukin IL28B[14] gene that infected patients present affect the degree of sensitivity to interferon, and therefore the extent of response to treatment with pegylated interferon and ribavirin. In the case of genotype 1a, the presence of the Q80K viral polymorphism is associated to a poorer response to treatment with simeprevir plus pegylated interferon and ribavirin.[15]

Finally, the hepatologist should evaluate the severity of liver damage, a key factor in determining management strategy (indication, posology and treatment duration), and patient follow-up.

While a liver biopsy is still considered as the gold standard for evaluation of the stage of fibrosis and disease progression, other less invasive procedures can now be used. Transition elastography obtained through the Fibroscan helps to estimate the degree of liver rigidity, which is correlated to the stage of fibrosis. This is a relatively simple, fast and painless technique that can accurately distinguish patients with no or mild fibrosis (F0-1) from those presenting advanced fibrosis or cirrhosis (F4), although it is less precise in intermediate stages of fibrosis (F2-3). There are technical limitations to elastography especially in obese patients (which require special tests), patients with acute hepatitis or those with liver stasis.

Figure 2. Diagnostic algorithm for patients with HCV antibodies.



*Repeat RNA testing if there is suspicion that the patient was exposed to HCV 6 months before and in case of incidences in the storage or processing of sample.

Indirect serological markers of liver fibrosis can also be used to estimate the degree of fibrosis. These include Fibrotest (obtained from GGT, bilirrubin, alpha-2 macroglobulin, haptoglobin and apolipoprotein 1) or Forns indexes (from platelet values, GGT, cholesterol and age) and the APRI (platelets and AST) which combined with elastography reduce the probability of overestimating or underestimating fibrosis that the Fibroscan may produce in some occasions.[16,17]

Treatment

The aim of treating HCV infection is to obtain a sustained viral response, defined as ongoing lack of detectable virus (negative viremia) 3-6 months after completion of treatment. sustained viral response is associated with a favourable clinical evolution,[18] an improvement in prognosis and quality of life,[19] and lack of disease progression.

The probability of attaining sustained viral response is related to the viral genotype, the degree of liver fibrosis and the patient's clinical situation with respect to previous treatments (naïve patients or prior relapse patients, partial responders or non-responders).

The era of standard IFN-α and ribavirin

In 1991, the FDA approved alpha interferon (IFN-α), a drug that modulates the immune response against HCV, for treatment of HCV. INF-α administered three times a week obtained overall sustained viral response in 8-12% of patients treated for 24 weeks[20] that increased when treatment was prolonged up to 48 weeks.[21] Sustained viral response rates in patients with viral genotype 1 treated with IFN-α for 24 weeks were even lower, around 2%. In 1998, ribavirin, an oral nucleoside analogue was approved. When ribavirin is used together with IFN-α in regimens of 24-48 weeks' duration, the sustained viral response rate increases to 38-43%, although the underlying mechanism of action is not clearly known.[22,23]

The pegylated IFN-α and ribavirin era

In 2001, pegylated interferon alpha (PegIFN-α) was approved for marketing. PegIFN-α fixes the interferon molecule to a chemical structure of the family of polyethylene glycols (PEG), leading to a slower elimination rate, and reducing the number of administrations per week from three times to once only. This formulation also avoids fluctuations in IFN levels and results in more stable plasma levels throughout the week,[24] which increases the

sustained viral response when associated with ribavirin, in comparison to standard IFN plus ribavirin.[25,26] However the overall sustained viral response has reached 76-82% in genotypes 2 and 3, but only 42-46% in genotype 1.[11,12]

The combination of PegIFN-α and ribavirin became the standard treatment option for chronic hepatitis C for approximately 10 years. The use of this regimen in recent years has also led to the discovery that patients with polymorphism CC of the IL28B were more likely to obtain sustained viral response.

This treatment is associated with many adverse reactions including severe effects such as liver decompensation, sepsis, immunosuppression, and psychiatric disorders including anxiety, depression and insomnia.[27]

Direct acting antivirals

Triple therapy

The approach to chronic hepatitis C management changed in 2001 with the approval of first generation viral protease inhibitors NS3/4A,[28,29] boceprevir,[30,31] and telaprevir[32,33] that block viral replication. These direct acting antiviral agents, effective only in genotype 1 patients, co-administered with pegIFN-α and ribavirin (triple therapy) increased sustained viral response up to 70% although response varied according to the subtype, IL28B polymorphism, type of response to previous treatment and severity of liver damage.

Some observational studies of triple therapy showed unexpected toxicity, clearly higher than that reported in phase III trials.[34,35] The association of these first generation protease inhibitors with PegIFN-α and ribavirin increased the incidence of adverse effects (especially anaemia and severe exanthema) as compared with use of Peg-IFN-α plus ribavirin alone. Patients with advanced fibrosis or cirrhosis were more likely to develop severe effects and even had a higher mortality rate.[29]

The revolution of the direct acting antiviral agents

An extensive programme of clinical and preclinical development has led to marketing of new direct acting antiviral drugs in four different classes: the second wave NS3/4A protease inhibitors, NS5A inhibitors and NS5B polymerase inhibitors (nucleos(t)ide analogues and non-analogue nucleos(t)ides).

Between 2014-2015 some of the new direct acting antiviral drugs have been authorized for clinical use in patients with genotypes 1 and 4, with cure rates around 90%.[36,37] It is expected that in the near future other pan-genotype direct acting antiviral drugs will be commercialized with a probability of obtaining sustained viral response in all patients between 85-100% with short treatment regimens and fewer adverse effects.[38]

Genotype 1 is most frequently present in Spain (70%) followed by genotype 3 (20%), genotype 4 (8%) and genotype 2 (3%)

Currently available drugs include simeprevir, second wave specific NS3/4A protease inhibitor sofosbuvir, nucleoside NS5B polymerase inhibitors,[39] daclatasvir,[40] ledipasvir,[41] and NS5A nucleoside polymerse inhibitors.

These drugs were included in treatment guidelines in 2014 in association with PegIFN-α, ribavirin and a direct acting antiviral drug. One of the latter was simeprevir (150mg daily) indicated in cases of genotype 1 and 4, based on the results of the QUEST-1 and QUEST-2 trials. Sustained viral response rates were 80% and 81% respectively.[42,43] Another combination included PegIFN-α, ribavirin and sofosbuvir (400mg daily). In the NEUTRINO trial, sustained viral response after 12 weeks was 89% in genotype 1 (92% in subtype 1a and 82% in subtype 1b) and 96% in patients with genotype 4.[44]

The COSMOS study evaluated the use of an "interferon free" combination of sofosbuvir and simeprevir in genotype 1 patients.[45] In the first cohort, non-responding patients with grade F0-F2 fibrosis showed sustained viral response rates of 96% and 93% after 12 weeks, and 79% and 93% after 24 weeks with and without ribavirin respectively. In the second cohort of naïve and previously treated patients with fibrosis grades F3-F4, sustained viral response rates were 93% and 93% after 12 weeks, and 79% and 93% after 24 weeks, with and without ribavirin, respectively. However, results in clinical practice show slightly lower rates than those in the COSMOS study, with sustained viral response rates reaching 82% after 12 weeks in the TRIO cohort and 89% after 4 weeks in the TARGET cohort.[46,47]

A combination of sofosbuvir and ribavirin for 12 weeks of therapy has been accepted as the standard treatment for genotype 2 patients,[48] although in previously treated individuals or those with cirrhosis, longer treatment is needed (between 16 and 20 weeks).[49] In patients with genotype 3 without cirrhosis, 24 weeks of treatment is used.

In late 2014 and early 2015, two new "interferon free" regimens were approved for the management of patients with genotypes 1 and 4. The first one was a combination of sofosbuvir (400mg) with ledipasvir (90mg) in one tablet taken once daily with or without ribavirin, depending on the severity of liver disease. The other regimen included

triple therapy with paritaprevir, ritonavir and ombitasvir (50mg/75mg/12.5mg per tablet; 2 tablets a day) which combines 2 antiviral agents with different mechanisms of action and with no overlapping resistance profiles that act at different points of the replication cycle of genotype 1 and 4 of the hepatitis C virus.[50] In genotype 1, this effect is potentiated by the association with dasabuvir (250 mg tablets, 2 tablets a day), a NS5B nucleoside polymerase inhibitor.[51] Sustained viral response rates with these two new regimens were above 90% and the drugs were very well tolerated.[52,53,54]

The growing and extraordinary progress in the development of these drugs for the management of chronic hepatitis C infection has led to challenges for the clinician in deciding on the best approach for each patient on the basis of virus genotypes, fibrosis degree and clinical status.

The development of direct acting antiviral drugs represents a major treatment advance. A major disadvantage, however, is the exorbitant cost of these treatments, which precludes immediate management of all HCV patients. For this reason, an orderly strategy is needed to allow patients to gain access to treatment. A National Strategic Plan for the management of Hepatitis C,[55] has been elaborated according to which all patients with chronic hepatitis C infection, monoinfected or HIV coinfected, naïve or non-responders to a previous antiviral treatment (independent of the type of treatment received) should all be considered for antiviral therapy.

However, although the price of direct acting antiviral drugs has markedly decreased over the last few months, their cost still remains very high, varying according to the genotype and the number of antiviral drugs used. Given these cost constraints and the prevalence of HCV infection in Spain, patients with significant liver fibrosis and/or clinically relevant extra-hepatic manifestations have been given priority with regard to access to these treatments.

Based on these criteria, priority groups of patients for oral direct acting antiviral drugs include:

- Patients with advanced liver fibrosis (F2-F4) regardless of the existence or not of previous liver related complications.
- Patients on the waiting list for liver transplant.
- Patients with liver transplant with a relapse of the infection in the liver graft, regardless of the existence of complications and the degree of fibrosis.
- Patients who have not responded to triple therapy with first generation protease inhibitors (boceprevir or telaprevir).
- Patients with organ transplants (other than the liver) with hepatitis C, regardless fibrosis degree.
- Patients with hepatitis C with extrahepatic HCV manifestations that are clinically relevant, regardless fibrosis degree.

In patients with F0-F1 fibrosis, treatment indications can differ on an individual basis. Treatment is indicated in patients at a high risk of infection or in fertile women desiring children, regardless of degree of fibrosis.

The new antivirals produce negative viremia after 12 weeks of treatment in more than 90% of patients

Different management options have been defined based on HCV genotypes and the stage of fibrosis (Table 1). These proposals are based on an analysis of approved product information, the reports issued by the Spanish Medicines Agency and the currently available scientific evidence.

Limitations of the current scientific evidence

The new drugs to treat the chronic HCV infection represent an important improvement in efficacy and disease management. However, there are some limitations in the clinical trial evidence that may overestimate the efficacy of these drugs in clinical practice, namely:

- The trials were carried out in patients with a good prognosis (potentially good responders), specifically younger patients (around 50 years old on average) with no previous treatments or treatment failure, no HIV coinfection, etc. results in other types of patients could be somewhat inferior.
- The sample size of the trials is very small, leading to an imprecise estimate of efficacy.
- The majority of the studies are open-label or phase 2 trials.
- Sustained viral response has been evaluated in the short-term, 12 weeks after completing treatment. The definition of sustained viral response is a lack of detectable virus 12-24 weeks after completion of treatment, but the trials have opted for the lower limit of this interval. HCV is a chronic infection and longer term results, over several years, should also be considered.
- It remains unknown whether survival is prolonged in patients with advanced disease (cirrhosis, hepatocellular carcinoma, patients awaiting liver transplant) for whom sustained viral response has been achieved.

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Conclusions

The management scenario for patients with chronic hepatitis C infection is promising.

However clinical trials have important limitations that might overestimate the real efficacy of these drugs in clinical practice.

Although newer treatments have fewer adverse effects as compared with previous therapies, there is a greater risk of drug interactions as treatment is being offered to older patients with advanced disease, and co-morbidities, who are taking a range of other treatments. This warrants for multidisciplinary approach and constant updating of the evidence when making clinical decisions.

Mid-to long-term results of these treatments are unknown, and so is the evolution of patients who are cured of the infection but already have advanced fibrosis.

The high cost of treatment and the high prevalence of HCV infection have made it necessary to prioritize candidates for treatment. Treatment should be less expensive to allow for universal access to drug therapy.

Table 1. Management options for chronic HCV infection.

NO CIRRHOSIS		
Genotype	**Treatment**	**Duration (weeks)**
G1a	OMT/PTV/r + DSV + RBV	12
	LDV/SOF	8-12[A]
G1b	OMT/PTV/r + DSV	12
	LDV/SOF	8-12[A]
G2	SOF + RBV	12
G3	SOF + DCV ± RBV	12
	SOF + RBV	24
G4	OMT/PTV/r + RBV	12
	LDV/SOF ± RBV	12
G5-6	LDV/SOF ± RBV	12
CIRRHOSIS Child-Pugh A		
Genotype	**Treatment**	**Duration (weeks)**
G1a	OMT/PTV/r + DSV + RBV	24
	LDV/SOF + RBV	12
G1b	OMT/PTV/r + DSV +RBV	12
	LDV/SOF + RBV	12
	LDV/SOF	24
G2	SOF + RBV	12-16[B]
G3	SOF+PR	12
	SOF + DCV + RBV	24
G4-6	LDV/SOF + RBV	12
	LDV/SOF	24
CIRROSIS Child-Pugh B-C		
Genotype	**Treatment**	**Duration (weeks)**
G1, G4, G5 and G6	LDV/SOF + RBV	12
	LDV/SOF	24
G2	SOF + RBV	16
G3	SOF + DCV + RBV	24

OMT: ombitasvir; PTV/r: paritaprevir/ritonavir; DSV: dasabuvir; RBV: ribavirin; LDV: ledipasvir; SOF: sofosbuvir; DCV: daclatasvir.
A: In naive patients, with RNA<6x106UI/mL treatment duration can be reduced to 8 weeks.
B: Extend treatment to 16 weeks in previously treated patients with cirrhosis.

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