

Treatment guidelines for Hepatitis C in Spain

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ABSTRACT

The discovery of new orally administered drugs that can block different targets of the replication cycle of the hepatitis C virus (HCV) with major antiviral activity, has revolutionized treatment of this infection and relegated interferon-based treatments to a secondary position. The start up of the National Strategic Plan for Combating Hepatitis C, which acknowledges the greater efficacy and safety of oral antiviral drugs, as well as the agreements between the pharmaceutical companies and different government bodies has enabled the initial difficulties of access to these medicines due to their high cost to be overcome.

In this rapidly changing environment, the availability of a therapeutic guide based on a critical analysis of the available evidence, takes on special relevance and provides a basic support for medical practitioners involved in HCV treatment.

However, the speed with which new therapeutic options are included and the limited evidence in some clinical scenarios signifies a challenge for those responsible for scientific societies whose job it is to coordinate the preparation of therapeutic guides and to keep recommendations up to date.

In this review we analyze the treatment recommendations for HCV in a consensus document drawn up by the Spanish Association for the Study of Liver Diseases (AEEH), to contrast them with recommendations given by American and European associations that study hepatic diseases.

Key words: Hepatitis C; Antiviral Agents; Prisons; Administration, Oral; Antiviral Agents; Hepacivirus; Spain; Efficacy.

Text received on: 04/28/2015

Text accepted on: 05/23/2015

INTRODUCTION

The aim of the guidelines is to produce therapeutic recommendations based on critical analysis of the published information that facilitate the clinical application of the available therapeutic alternatives. The speed with which orally administered drugs (OADs) for HCV infection have arisen, related administrative obstacles and heterogeneous access to these drugs have entailed a huge challenge for those responsible of updating treatment guidelines. This has also conditioned that recent updates included less effective or more toxic therapeutic regimens which were sometimes the only alternative available (for instance, GeSIDA-GEHEP guidelines¹, which are currently being reviewed). It is therefore desirable that the implementation of the National Strategic Plan for Combating Hepatitis C, which acknowledges the greater efficacy and safety of oral antiviral drugs, as well as the agreements between the pharmaceutical companies and

different government entities, enables inequalities to be overcome and the standardization of therapeutic indications to be achieved.

In this review, we take the recently published consensus document² drawn by the Spanish Association for the Study of Liver Diseases (AEEH) as a reference and we compare it with the recommendations issued by the European Association for the Study of the Liver (EASL)³ and the recommendations drawn up jointly by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA)⁴. All of them include recommendations applicable to both HCV mono-infected patients and HCV-HIV coinfecting patients.

WHO SHOULD BE TREATED?

Generally speaking, it is indicated to initiate therapy in all patients infected with HCV. However,

treatment priority should be given to patients with advanced fibrosis; clinical manifestations of the infection and as secondary prophylaxis (see Table1). This ranking of priority enables the rational administration of new drugs, which ultimately should aim the eradication of HCV.

NEW ORAL HCV DRUGS

Simeprevir is a protease inhibitor with a similar efficacy against genotype 1 to Telaprevir yet less toxic and active against genotype 4 too. Together with Peg-IFN and Ribavirin (PR) it is still recommended by the AEEH and the EASL for the treatment of genotypes 1 and 4. However, in view of its toxicity and the availability of more effective combinations, its use should be exceptional or at least discouraged, as established by the AASLD/IDSA. Simeprevir together with Sofosbuvir has shown high efficacy against genotype 1 and is probably an effective combination against genotype 4 but we lack clinical information.

Sofosbuvir is a nucleotide analogue polymerase inhibitor with pan-genotypic activity and in comparison with the rest of oral HCV drugs it has a high genetic barrier therefore included in most of currently used regimens. Together with PR is a therapeutic alternative for genotype 1 and 4 patients. However, the availability of more effective combinations, especially for treatment-experienced patients and those with advanced fibrosis relegates sofosbuvir plus PR to exceptional use. The only clinical circumstance under which sofosbuvir together with PR can be considered as a preferential option is in cirrhotic genotype 2 and 3 patients.

Ledipasvir is an inhibitor of NS5a replication complex active against genotypes 1 and 4, and to a lesser extent against genotype 3. It only exists as a co-formulation with Sofosbuvir, and therefore its use is influenced by the latter.

Daclatasvir is another NS5a inhibitor with pan-genotypic activity. It can be used, together with Sofosbuvir, in patients infected by any genotype and it is a preferential option for genotype 3 non-cirrhotic patients.

Drugs manufactured by Abbvie® are active against different viral targets: Paritaprevir/r (protease inhibitor co-dosed with Ritonavir); Ombitasvir (NS5a inhibitor) and Dasabuvir (non-nucleoside analogue polymerase inhibitor). They are indicated for genotype 1 patients (3D regimen: Paritaprevir/r-Ombitasvir and Dasabuvir) or for genotype 4 patients (2D regimen: Paritaprevir/r and Ombitasvir), in most of the cases (except for genotype 1b non-cirrhotic patients) in combination with Ribavirin (RBV).

In oral HCV regimens the analysis of IL28B and of primary resistances is not recommended. Finally, we should consider the risk of potentially dangerous interactions of oral HCV drugs and antiretroviral or co-administered drugs (for instance, with amiodarone there is a risk of extreme bradycardia). Please consult www.hep-druginteractions.org for further information.

RECOMMENDATIONS FOR GENOTYPE 1 PATIENTS

Sofosbuvir/Ledipasvir for untreated patients

The trial ION-1⁵ revealed that the rates of sustained virologic response (SVR) with this combination, with or without RBV, during 12 and 24 weeks, ranged between 97% and 100%. A total of 2 patients out of the 134 included had virologic relapse. Thus the recommendation of including RBV to all cirrhotic untreated genotype 1 patients included in the AEEH guidelines (see Table 1) and in those by the EASL is not based on clinical data.

Table 1: Therapeutic indications for HCV with new oral drugs

Priority treatment	Advanced fibrosis (F3-F4) including decompensated cirrhosis
	Pre or Post hepatic transplantation
	Extra-hepatic relevant manifestations (for instance cryoglobulinemia, vasculitis, intense fatigue, lymphoma)
	HBV or HIV co-infection or non-alcoholic steatosis
	High risk of transmission: IDUs, MSM, prisoners, pre-gestation
Justified treatment	Moderate fibrosis F2
Individualised indication	Fibrosis F0-F1 (treatment can be postponed)
Not recommended	Limited life expectancy due to other diseases

The trial ION-3⁶ compared an 8-week with and without RBV regimen with a 12 week regimen without ribavirin for naïve non-cirrhotic patients. The rate of SVR ranged between 93 and 95% and was similar for the three arms and hence the non-inferiority of the 8 week regimen was concluded. However, relapse rates were higher in the 8 week group (20/431) regardless of the use of RBV than in the 12 week group (3/216). Moreover, relapse rates were similar for patients with HCV ARN log10<6.7 MIU/mL with 8 (2/123) and 12 (2/131) week regimens. Guidelines recommend the use of Sofosbuvir/Ledipasvir for 8 weeks in non cirrhotic patients with predictors of a favorable response (see Table 2). Nevertheless, extrapolating these results to clinical practice should be done with extreme caution.

Sofosbuvir/Ledipasvir for previously treated patients

In the ION-2 trial, rates of SVR with this combination for 12 or 24 weeks with or without RBV in genotype 1 previously treated patients ranged between 94% and 99%⁷. In cirrhotic patients the rates of SVR12 were higher with the 24 week regimens (100% with or without ribavirin) when compared with the 12 week regimens (86% without RBV and 82% with RBV). Grouped analysis of 513 cirrhotic naïve- and experienced-treatment patients included in phase 2 and 3 clinical trials, revealed that 96% of cirrhotic patients with previous therapeutic failure achieved SVR12 after 12 weeks of sofosbuvir/ledipasvir plus ribavirin, and similar response rates were concluded for the 24 week regimen (with and without RBV)⁸.

The Sirius trial revealed that 96% of patients with compensated cirrhosis and previous therapeutic failure of PR+/- a protease inhibitor who underwent treatment with sofosbuvir/ledipasvir plus ribavirin for 12 weeks achieved SVR when compared with 97% of those who did so for 24 weeks⁹. These results suggest that for most of cirrhotic previously treated patients the regimen with sofosbuvir/ledipasvir plus ribavirin for 12 weeks can be enough (see Table 2). However, for patients who do not tolerate RBV or with advanced cirrhosis the optimal regimen should last 24 weeks, as recommended by the EASL and the AASLD/IDSA.

To conclude, sofosbuvir/ledipasvir plus ribavirin for 12 weeks achieved a rate of SVR > 95% in patients with a previous failure of sofosbuvir¹⁰.

Paritaprevir/Ritonavir-Ombitasvir and Dasabuvir for naïve treatment patients

In the SAPHIRE-I trial¹¹, 96% of previously untreated non cirrhotic patients treated with 3D plus RBV for 12 weeks achieved SVR: genotype 1a 95% and genotype 1b 98%. In another trial¹², 12 weeks of the 3D combination with and without ribavirin were compared in naïve non-cirrhotic patients. For subtype 1B the rate of SVR12 was 99% for both regimens with and without ribavirin and for subtype 1a 90% for the regimen without RBV and 97% for the one including RBV. These results justify the use of the 3D regimen without ribavirin in naïve non cirrhotic patients with subtype 1b HCV and the 3D regimen with RBV for subtype 1a patients (see Table 2). To conclude, the TURQUOISE-II trial¹³ compared the 3D combination plus ribavirin for 12 and 24 weeks in cirrhotic patients. 95% and 95% of previously untreated patients achieved SVR with no significant differences between both groups. The rates of SVR were 100% for genotype 1b in both arms and 92-93% for genotype 1a. These results justify the recommendation of the 3D plus RBV regimen for 12 weeks in cirrhotic previously untreated genotype 1b or 1a patients (see Table 2). Yet the EASL and American guidelines recommend, as in the drugs' fact sheet, to treat all cirrhotic genotype 1a patients for 24 weeks.

Paritaprevir/r-Ombitasvir and Dasabuvir in previously treated patients

This combination plus ribavirin for 12 weeks achieved rates of SVR of 96% in the SAPHIRE II trial¹⁴, in non cirrhotic previously treated with PR patients. The results were consistent for both genotype 1a patients (96%) and patients with previous null response (95%).

In previously treated genotype 1b cirrhotic patients included in the TURQUOISE-II trial¹³, no significant differences were observed among between the 12 week and the 24 week regimens, regardless of previous response. However, in genotype 1a patients the rates of SVR were inferior in patients with previous null response who underwent the 12 week regimen (40/50, 80%) than in the 24 week group (39/42, 93%). SVR rates for patients with previous virologic relapse were 93% (14/15) and 100% (13/13) and in patients with previous partial response 100% (11/11 and 10/10) after 12 and 24 weeks of treatment respectively.

Therefore, guidelines recommend the 3D regimen plus ribavirin for 12 weeks for previously treated

Table 2: Therapeutic recommendations for genotype 1 patients

PREVIOUSLY UNTREATED OR RELAPSE PATIENTS	
First-line options	Sofosbuvir/Ledipasvir (400/90 mg once per day) +/- Ribavirin 100-1200mg/day General recommendation: Sofosbuvir/Ledipasvir for 12 weeks For cirrhotic patients: Sofosbuvir/Ledipasvir + Ribavirin for 12 weeks For non cirrhotic patients with favorable response predictors: Sofosbuvir/Ledipasvir for 8 weeks
	Paritaprevir/r Ombitasvir + Dasabuvir (3D) +/- Ribavirin 100-1200mg/day a. Genotype 1b: 3D for 12 weeks (plus ribavirin in cirrhotic patients) b. Genotype 1a: 3D+Ribavirin for 12 weeks
	Sofosbuvir + Simeprevir +/- Ribavirin for 12 weeks
Second-line options	Sofosbuvir + Daclatasvir +/- Ribavirin for 12 weeks
	Sofosbuvir + Peg-interferon/Ribavirin for 12 weeks
Third-line options	Simeprevir + Peg-interferon/Ribavirin for 24 weeks ¹
PREVIOUS THERAPEUTIC FAILURE PATIENTS	
First-line options	Sofosbuvir/Ledipasvir +/- Ribavirin a. General recommendation: Sofosbuvir/Ledipasvir for 12 weeks. b. Cirrhotic patients or previous failure of Sofosbuvir: Sofosbuvir/Ledipasvir + Ribavirin for 12 weeks
	Paritaprevir/r- Ombitasvir + Dasabuvir (3D) +/- Ribavirin 1000-1200 mg/day (there is no information on this regimen for patients with previous failure of Boceprevir o Telaprevir ²) a. Genotype 1b: 3D for 12 weeks (in cirrhotic patients plus Ribavirin) b. Genotype 1a: 3D + Ribavirin for 12 weeks (in cirrhotic patients, for 24 weeks)
	Sofosbuvir + Simeprevir +/- Ribavirin for 12 weeks (poorly assessed in patients with previous failure of Boceprevir or Telaprevir ²)
Second-line options	Sofosbuvir + Daclatasvir +/-Ribavirin for 24 weeks
Third-line options	Sofosbuvir + Peg-interferon/Ribavirin for 12 weeks (recommendation based on real life cohorts, few patients with failure of triple therapy with Boceprevir or Telaprevir)

Discontinuing therapy in patients with detectable HCV RNA levels in week 4 of treatment. The more recommendable regimens for previous failure of triple therapy with Boceprevir or Telaprevir are Sofosbuvir/Ledipasvir and Sofosbuvir/Daclatasvir

non-cirrhotic subtype 1a or 1b patients. In cirrhotic previously treated subtype 1a patients, 24 weeks are recommended, regardless of previous response, although the grade of evidence for this recommendation for patients with previous relapse or partial response is poor¹³.

Sofosbuvir and Simeprevir

The COSMOS trial¹⁵ assessed this combination with and without ribavirin for 12 or 24 weeks. SVR12 rates were similar in naïve patients, 95% (38/40), and previously treated patients, 91% (116/127) and in the 12 week group, 94% (77/82) and the 24 week group, 91% (77/85), regardless of ribavirin. Grouped analysis including the ribavirin-free groups revealed that 95% (20/21) of patients with F0-F3 fibrosis treated for 12 weeks and 86% (6/7) of cirrhotic patients achieved SVR12. All cirrhotic patients (10/10) treated for 24 weeks achieved SVR12. All relapses occurred

among genotype 1a patients. We still do not know the role of ribavirin on the risk of relapse. In the HCV-TARGET 2.0 cohort¹⁶, 89% (269/303) of patients achieved SVR4 after 12 weeks of treatment with sofosbuvir and simeprevir +/- ribavirin: 92% (113/123) of non-cirrhotic patients; 87% (156/180) of cirrhotic patients and 75% (61/81) of patients with decompensated cirrhosis. No significant differences were observed between patients treated with ribavirin (87%) and without it (86%). The rates of SVR4 were 95% (88/93) in subtype 1b patients and 89% (154/180) in subtype 1a patients. Multivariate analysis revealed that hypoalbuminemia, genotype 1a, hepatic decompensated cirrhosis and previous failure of protease inhibitors were associated to a poorer response. In the TRIO cohort¹⁷, the rates of SVR12 with sofosbuvir and simeprevir, +/- ribavirin for 12 weeks were 88% (68/88) in naïve cirrhotic patients and 87% (64/74) and 76% (53/70) in previously treated non cirrhotic and cirrhotic patients respectively. The rate

of SVR12 was 82% in patients with previous therapeutic failure of protease inhibitors (n=33) and 80% with previous failure of PR (n=75).

These results suggest that the probability of responding to sofosbuvir and simeprevir with or without ribavirin is lower in patients with genotype 1a HCV, hepatic cirrhosis and most probably in patients with previous failure of protease inhibitors.

In recently published trials, sofosbuvir and simeprevir for 12 weeks achieved a high rate of SVR12 in genotype 1 non-cirrhotic patients, both naïve (97%) and experienced (95%)¹⁸. In cirrhotic patients the rate of SVR with sofosbuvir + simeprevir for 12 weeks is lower in previously treated patients (77%) than in naïve patients (85%) and in subtype 1a patients with Q80K polymorphism (74%) than in subtype 1a patients lacking this mutation (92%) or in subtype 1b patients (84%)¹⁹. If jointly considered, these results can help us extrapolating recommendations by different guidelines to clinical practice: sofosbuvir and simeprevir +/- ribavirin for 12 weeks, regardless of the degree of fibrosis (AEEH, Table 2); sofosbuvir and simeprevir for 12 weeks in non-cirrhotic patients and plus ribavirin or for 24 weeks in all cirrhotic patients (EASL) or 24 weeks in all cirrhotic patients with or without ribavirin (AASLD/IDSA).

Sofosbuvir and Daclatasvir

Ninety-eight percent (164/167) of non-cirrhotic patients treated with this combination with or without RBV, achieved SVR12, including 84 of the 85 patients treated for 24 weeks: 44 naïve patients and 40 out of 41 patients with previous failure of PR and boceprevir or telaprevir. 98% (80/82) of naïve patients treated for 12 weeks achieved SVR12²⁰.

In the ALLY-2 trial 96% (80/83) of naïve patients and 98% (43/44) of previously treated patients (15 of whom presented hepatic cirrhosis) achieved SVR after 12 weeks of treatment with sofosbuvir and daclatasvir without ribavirin²¹.

In the ALLY-1 trial²², 82% (37/45) of patients (60% of whom had been previously treated) with decompensated cirrhosis treated with sofosbuvir, daclatasvir and ribavirin (initial dose of 600mg per day) for 12 weeks achieved SVR12.

In the AEEH document sofosbuvir and daclatasvir with or without ribavirin are recommended as second therapeutic alternatives for 12 weeks in naïve patients and for 24 weeks in previously treated patients (Table 2). The EASL recommends sofosbuvir and daclatasvir without ribavirin for 12 weeks in non-cirrhotic patients and plus ribavirin or for 24 weeks in

cirrhotic patients. Daclatasvir has not been approved by the FDA and is therefore not included in the American guidelines.

Sofosbuvir and PR

In the NEUTRINO trial²³, 89% of naïve patients treated with this regimen for 12 weeks achieved SVR: 92% (207/225) of subtype 1a patients; 82% (54/66) of subtype 1b patients; 80% of cirrhotic patients and 92% of non-cirrhotic patients. In the TRIO cohort, the rate of SVR12 in naïve patients was 77%. In previous failure patients: 77% (30/39) in non-cirrhotic patients and 62% (53/85) in cirrhotic patients. In patients with virologic relapse after PR treatment, sofosbuvir together with PR achieved a rate of SVR12 of 80%²⁴.

In another trial, sofosbuvir + PR were inferior to simeprevir + sofosbuvir in genotype 1a patients with compensated cirrhosis, both in naïve and previously treated patients with null response²⁵.

In the document by the AEEH this regimen is considered a second option therapeutic alternative in previously untreated genotype 1 patients (Table 2). The EASL considers it a suitable alternative for both naïve and previously treated patients and its use is not recommended by the AASLD/IDSA.

Simeprevir and PR

The rates of SVR in naïve patients according to the registered trials were 80% (210/264)²⁶ and 81% (209/257)²⁷: 85% (228/267) for subtype 1b; 84% and 58% in subtype 1a patients without and with Q80K polymorphism respectively; 84% (317/378) in F0-F2 fibrosis patients; 73% (60/82) in F3 patients and 60% in F4 patients.

In previously treated patients the rate of SVR with simeprevir and PR was: 70% (163/234) in patients with previous partial response and 44% (63/145) in patients with previous null response²⁸.

This regimen is considered as a third-choice alternative in the AEEH recommendations (Table 2) and is considered a valid alternative for both naïve and experienced patients according to the EASL. Its use is not recommended by the AASLD/IDSA.

RECOMMENDATIONS FOR GENOTYPE 2 PATIENTS

Sofosbuvir and Ribavirin

Between 86% and 97% of patients treated with sofosbuvir and ribavirin for 12 weeks achieved

SVR^{23, 29-30}. The Photon 2 trial revealed that 89% (17/19) of HIV co-infected genotype 2 naïve patients treated with that combination achieved SVR³¹. In the FUSION trial, previously treated patients achieved rates of SVR of 60% (6/10) in cirrhotic patients treated for 12 weeks and of 78% (7/9) in those treated for 16 weeks²⁹.

In the BOSON trial, the rate of SVR12 in genotype 2 previously treated cirrhotic patients treated with sofosbuvir and ribavirin for 16 and 24 weeks were 87% (13/15) and 100% (17/17) respectively³².

This is considered a first-line alternative by the AEEH (Table 3) with the recommendation of a 16 week regimen in cirrhotic previously untreated patients and a 16 to 24 week in previously treated patients, as recommended by other guidelines.

Sofosbuvir + PR for 12 weeks

The rate of SVR achieved with this regimen in 23 patients with previous failure of IFN/RBV was 96%, including 13 of 14 cirrhotic patients³³. In the BOSON trial, 94% (15/16) of genotype 2 cirrhotic previously treated patients achieved SVR12 after a 12 week regimen of sofosbuvir and PR³². This is a preferential option for previously treated patients according to AEEH (Table 3) and EASL guidelines and an alternative according to the AASLD/IDSA.

RECOMMENDATIONS FOR GENOTYPE 3 PATIENTS

Sofosbuvir and Ribavirin for 24 weeks

In the VALENCE trial, 85% (212/250) of patients achieved SVR with this regimen, similar to naïve non

cirrhotic patients (95%) and cirrhotic patients (92%). In previously treated patients 87% (87/100) of non-cirrhotic patients and 62% of cirrhotic patients did so³⁰.

In the PHOTON 2 trial, 89% (97/106) of HIV co-infected patients obtained SVR: 86% (49/57) of previously untreated patients and 78% (18/23) of previously treated patients³¹. The results of the BOSON trial³² reveal lower rates of SVR12 in previously treated patients than in naïve patients (80% vs. 88%) and in cirrhotic patients than in non-cirrhotic patients (79% vs. 97%). These results justify the recommendations displayed in Table 3.

Sofosbuvir and Daclatasvir

The combination of sofosbuvir and daclatasvir for 12 weeks obtained rates of SVR of 97% and 94% in non cirrhotic naïve and previously treated patients respectively. In cirrhotic patients the rate of SVR was 58% in naïve patients and 69% in previously treated patients³⁴. An observational study concluded that 70% of patients (n=114) suffering from decompensated cirrhosis (Child-Pugh ≥7) achieved SVR12 after a 12 week regimen of this combination plus ribavirin³⁵. The Spanish guidelines recommend the addition of ribavirin and/ or a 24 week regimen in cirrhotic patients (Table 3).

Sofosbuvir/Ledipasvir and Ribavirin for 12 weeks

64% (16/25) of naïve patients treated with sofosbuvir/ledipasvir for 12 weeks (n=3 cirrhotic patients) achieved SVR in comparison with 100% (26/26) of those treated with sofosbuvir/ledipasvir plus ribavirin (n=5 cirrhotic patients)³⁶.

Tabla 3. Recomendaciones de tratamiento en pacientes con genotipo 2 y 3.

Genotype 2	
Untreated or previous relapse patients	Sofosbuvir + Ribavirin for 12 weeks (16 weeks in cirrhotic patients)
Options for previous therapeutic failure	Sofosbuvir + Peg-interferon/Ribavirin for 12 weeks
	Sofosbuvir + Ribavirin for 16-24 weeks
Genotype 3	
Previously untreated patients	Sofosbuvir + Peg-interferon/Ribavirin for 12 weeks
	Sofosbuvir + Ribavirin for 24 weeks
	Sofosbuvir + Daclatasvir, 12 weeks (not recommended in cirrhotic patients)
	Sofosbuvir/Ledipasvir + Ribavirin for 12 weeks
Previously treated patients	Sofosbuvir + Peg-interferon/Ribavirin for 12 weeks
	Sofosbuvir + Daclatasvir 12 weeks (in cirrhotic patients it is recommended to extend treatment 24 weeks or to add Ribavirin)
	Sofosbuvir/Ledipasvir + Ribavirin for 12 weeks

In previously treated patients the rate of SVR12 was 82% (41/50): 73% (16/22) in cirrhotic patients and 89% (25/28) in non-cirrhotic patients³⁷. According to these results, with a poor degree of evidence this combination is considered a therapeutic alternative in genotype 3 patients in the AEEH guidelines (Table 3) but is not recommended by either European or American guidelines.

Sofosbuvir and PR for 12 weeks

In the LONESTAR-2 trial³³, 83% (20/24) of previously treated patients achieved SVR with this combination, including 10/12 cirrhotic patients. In another trial which included 22 patients with previous failure of sofosbuvir and ribavirin, 91% achieved SVR³⁸.

In the BOSON trial³², 93% (168/181) of genotype 3 patients achieved SVR12 after a 12 week treatment of sofosbuvir and PR. The rate of SVR12 was 86% (30/35) in previously treated cirrhotic patients, therefore justifying the preferential use of this regimen in these patients (see Table 3).

RECOMMENDATIONS FOR GENOTYPE 4 PATIENTS

Sofosbuvir and Ribavirin for 24 weeks

In Egyptian patients³⁹, the efficacy of sofosbuvir and ribavirin in a 24 week regimen was superior than the 12 week regimen both in naïve patients (100%, 14/14 vs. 79% 11/14) and in previously treated patients (93% 14/15 vs. 59% 10/17). These results were confir-

med by another trial with a comparable population⁴⁰. In the PHOTON 2 trial, 84% (26/31) of co-infected genotype4 naïve patients achieved SVR: 83% (19/23) of non-cirrhotic patients and 88% (7/8) of cirrhotic patients. This is considered a preferential option by the AEEH guidelines and those by the AASLD/IDSA but not in the EASL recommendations.

Paritaprevir/r - Ombitasvir + Ribavirin for 12 weeks

This combination achieved a rate of SVR of 100% in genotype 4 non-cirrhotic patients both naïve (n=42) and previously treated (n=49)⁴¹. Although both the AEEH and the EASL recommend extending the regimen to 24 weeks for cirrhotic patients we lack clinical information supporting this recommendation (Table 4).

Sofosbuvir/Ledipasvir for 12 weeks

This combination has been assessed in 21 patients (9 of whom had cirrhosis) with a rate of SVR of 95%⁴² and it is recommended as a first-line option, in spite of its poor degree of evidence, in all available guidelines (Table 4)

Sofosbuvir and PR for 12 weeks

The analysis of genotype 4 patients included in the NEUTRINO trial²³ revealed a rate of SVR12 of 96% (27/28). We lack information regarding its efficacy in cirrhotic and previously treated patients.

Table 4: Therapeutic recommendations for genotype 4 patients

PREVIOUSLY UNTREATED OR RELAPSE PATIENTS	
First-line options	Sofosbuvir/Ledipasvir for 12 weeks
	Paritaprevir/r + Ombitasvir + Ribavirin for 12 weeks (24 weeks in cirrhotic patients).
	Sofosbuvir + Ribavirin for 24 weeks.
Second-line options	Sofosbuvir + Simeprevir for 12 weeks (lack of results obtained in clinical practice)
	Sofosbuvir + Peg-interferon/Ribavirin for 12 weeks
	Sofosbuvir + Daclatasvir for 12 weeks (24 weeks in cirrhotic patients).
Third-line options	Simeprevir + Peg-interferon/Ribavirin for 24-48 weeks
	Daclatasvir + PR for 24 weeks
PREVIOUS THERAPEUTIC FAILURE PATIENTS	
First-line options	Sofosbuvir/Ledipasvir for 12 weeks.
	Paritaprevir/r + Ombitasvir + Ribavirin for 12 weeks in non-cirrhotic patients.
Second-line options	Sofosbuvir + Ribavirin for 24 weeks.
	Sofosbuvir + Daclatasvir 12 weeks (24 weeks in cirrhotic patients).
Third-line options	Sofosbuvir + Simeprevir for 12 weeks.

Simeprevir + PR for 24-48 weeks

This combination achieved rates of SVR of 83% (29/35) among naïve patients; 86% (19/22) in relapse patients, 60% (6/10) in partial responders and 40% (16/40) in null responders. In cirrhotic naïve and relapse patients the rate of SVR was 72% (8/11) and in null responders 36% (5/14)⁴³.

Daclatasvir + PR

Eighty-two percent (67/82) of naïve patients who underwent this treatment for 24 to 48 weeks obtained SVR; 78% (7/9) of whom were cirrhotic patients. 67% (55/82) of patients obtained SVR after 24 weeks of treatment⁴⁴.

PR based regimens with sofosbuvir, simeprevir and daclatasvir, specially the last two, are more complex and less effective than other available alternatives and although included in the AEEH and the EASL recommendations, its use should be exceptional.

OTHER REGIMENS

Last and in spite of the lack of clinical information on the efficacy of sofosbuvir together with simeprevir or daclatasvir in genotype 4 patients, guidelines extrapolate data obtained from genotype 1 patients and thus they are recommended as therapeutic alternatives.

To conclude, the approval of new oral HCV drugs has enabled the elaboration of highly effective regimens for most clinical scenarios. The degree of evidence for some of the recommendations however is limited and it justifies the differences observed among guidelines. The involvement of pharmaceutical companies, the administration and medical practitioners is of paramount importance for the implementation of a strategic plan which includes a rational use of new oral HCV drugs and which gives priority to patients at higher risk of progression, or in specific groups as a measure of secondary prophylaxis to achieve, in the medium term, the eradication of HCV infection.

Different scientific societies now face the challenge of updating treatment guideline to include the therapeutic innovations which are quickly arising. It would be desirable to sum up, that there was a reference document in Spain for all professionals involved in the treatment of Hepatitis C.

ACKNOWLEDGEMENTS

To Dr. Jordi Navarro for his critical review of this paper.

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