**Name of journal:** **World Journal of** **Gastroenterology**

**ESPS Manuscript NO: 19254**

**Manuscript Type: TOPIC HIGHLIGHTS**

2015 Advances in Hepatitis C virus

**New approaches in the treatment of hepatitis C**

González-Grande R *et al.* New treatments of hepatitis C

Rocío González-Grande, Miguel Jiménez-Pérez, Carolina González Arjona, José Mostazo Torres

**Rocío González-Grande, Miguel Jiménez-Pérez, González Arjona , José Mostazo Torres,** Liver Transplantation and Hepatology Unit, UGC de Aparato Digestivo, Hospital Regional Universitario, Malaga 29010, Spain

**Author contributions:** Jiménez-Pérez M, González-Grande R, Mostazo Torres J, and González Arjona C contributed equally to this work.

**Conflict-of-interest statement:** The authors have no conflict of interest to report.

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**Correspondence to: Miguel Jiménez-Pérez, MD,** UGC de Aparato Digestivo, Unidad de Hepatología-Trasplante Hepático, Hospital Universitario Regional de Málaga, Avenida Carlos Haya, 29010 Malaga, Spain. [mjimenezp@commalaga.com](mailto:mjimenezp@commalaga.com)

**Telephone**: +34-61-095935

**Fax**: +34-95-1291941

**Received:** May 1, 2015

**Peer-review started:** May 8, 2015

**First decision:** July 14, 2015

**Revised:** August 5, 2015

**Accepted:** October 12, 2015

**Article in press:**

**Published online:**

**Abstract**

About 130-170 million people, is estimated to be infected with the hepatitis C virus (HCV). Chronic HCV infection is one of the leading causes of liver-related death and in many countries it is the primary reason for having a liver transplant. The main aim of antiviral treatment is to eradicate the virus. Until a few years ago the only treatment strategy was based on the combination of pegylated interferon and ribavirin (PEG/RBV). However, in genotypes 1 and 4 the rates of viral response did not surpass 50%, reaching up to 80% in the rest. In 2011 approval was given for the first direct acting antiviral agents (DAA), boceprevir and telaprevir, for treatment of genotype 1, in combination with traditional dual therapy. This strategy managed to increase the rates of sustained viral response (SVR) in both naive patients and in retreated patients, but with greater toxicity, interactions and cost, as well as being less safe in patients with advanced disease, in whom this treatment can trigger decompensation or even death. The recent, accelerated incorporation since 2013 of new more effective DAA, with pan-genomic properties and excellent tolerance, besides increasing the rates of SVR (even up to 100%), has also created a new scenario: shorter therapies, less toxicity and regimens free of PEG/RBV. This has enabled their almost generalised applicability in all patients. However, it should be noted that most of the scientific evidence available is based on expert opinion, case-control series, cohort studies and phase 2 and 3 trials, some with a reduced number of patients and select groups. Few data are currently available about the use of these drugs in daily clinical practice, particularly in relation to the appearance of side effects and interactions with other drugs, or their use in special populations or persons with the less common genotypes. This situation suggests the need for the generalised implementation of registries of patients receiving antiviral therapy. The main inconvenience of these new drugs is their high cost. This necessitates selection and prioritization of candidate patients to receive them, via strategies established by the various national organs, in accordance with the recommendations of scientific societies.

**Key words**: Hepatitis C; Treatment; Direct acting antiviral agents; Patients; Outcome

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**Core tip:** About 130-170 million people, is estimated to be infected with the hepatitis C virus. Chronic hepatitis C is one of the leading causes of liver-related death and in many countries it is the primary reason for having a liver transplant. Until a few years ago the only treatment strategy was based on the combination of pegylated interferon and ribavirin. Since 2011 the accelerated incorporation of direct acting antiviral agents has created a new scenario: increasing the rates of sustained viral response, shorter therapies, less toxicity and regimens free of interferon and/or ribavirin and can even modify the natural history of the disease.

González-Grande R, Jiménez-Pérez M, González Arjona C, Mostazo Torres J. New approaches in the treatment of hepatitis C. *World J Gastroenterol* 2015; In press

**INTRODUCTION**

About 3% of the world population, some 130-170 million people, is estimated to be infected with the hepatitis C virus (HCV). Of these, 55%-85% will develop chronic hepatitis, 30% will later have cirrhosis, and 2% will have hepatocarcinoma[1]. Chronic HCV infection is one of the leading causes of liver- related death and in many countries it is the primary reason for having a liver transplant.

The main aim of antiviral treatment is to eradicate the virus, defined as a viralRNA that is undetectable by highly sensitive methods (lower detection limit of 15 IU/mL). There is considered to be a sustained viral response (SVR) if this RNA remains undetectable 12 wk after ceasing treatment (SVR12).

Until a few years ago the only treatment strategy was based on the combination of pegylated interferon and ribavirin (PEG/RBV) for 24 or 48 wk depending on the genotype. However, in genotypes 1 and 4 the rates of viral response did not surpass 50%, and were only slightly higher in the other genotypes.

Better understanding of the replication cycle of HCV has led to the identification of new therapeutic targets. In 2011 approval was given for the first direct acting antiviral agents (DAA), boceprevir and telaprevir, for treatment of genotype 1, in combination with traditional dual therapy[2,3]. This strategy managed to increase the rates of SVR in both naive patients and in retreated patients, but with greater toxicity, interactions and cost, as well as being less safe in patients with advanced disease, in whom this treatment can trigger decompensation or even death[4].

The recent, accelerated incorporation since 2013 of new more effective DAA, with pan-genomic properties and excellent tolerance, besides increasing the rates of SVR (even up to 100%), has also created a new scenario: shorter therapies, less toxicity and regimens free of interferon and/or ribavirin. This has enabled their almost generalised applicability in all patients[5].

However, it should be noted that most of the scientific evidence available is based on expert opinion, case-control series, cohort studies and phase 2 and 3 trials, some with a reduced number of patients and select groups. Few data are currently available about the use of these drugs in daily clinical practice, particularly in relation to the appearance of side effects and interactions with other drugs, or their use in special populations or persons with the less common genotypes[6]. This situation suggests the need for the generalised implementation of registries of patients receiving antiviral therapy.

The main inconvenience of these new drugs is their high cost. This necessitates selection and prioritization of candidate patients to receive them, *via* strategies established by the various national organizations, in accordance with the recommendations of scientific societies.

The purpose of this article is to review the drugs currently available for the treatment of hepatitis C and update the recommendations according to the genotype.

**DIRECT ACTING ANTIVIRAL AGENTS**

***DAA currently available***

The US Food and Drug Administration (FDA) has approved the following, currently commercialised DAA:

**Sofosbuvir (Sovaldi):**a nucleotide NS5B polymerase inhibitor, essential for viral replication. The dose is 400 mg (one pill) per day. This is a prodrug that undergoes intracellular metabolism to form its active metabolite. In 2013 the FDA approved its use for the treatment of HCV. Although its action is pan- genotypic, it is approved for genotypes 1, 2, 3 and 4 but always in combination with other DAA or with PEG/RBV, never in monotherapy[7].

**Simeprevir (Olysio):** a pan-genotypic NS3/4a protease inhibitor that intervenes in the HCV life cycle. The dose is 150 mg (one capsule) per day. The FDA approved it in 2014 for the treatment of genotype 1 HCV, in combined therapy. In genotype 1a patients, the presence of the Q80K polymorphism is associated with a significant reduction in SVR12 in patients treated with simeprevir+PEG/RBV. In these cases, therefore, alternative treatment is recommended[8].

**Daclatasvir (Daklinza):**non-structural NS5A protein inhibitor that forms part of the viral replication complex. It also inhibits virion assembly. The dose is 60 mg (two pills) once a day. The FDA approved its use in 2014 for HCV genotypes 1, 3 and 4[9].

**Sofosbuvir + ledipasvir (Harvoni):**combination of sofosbuvir (400 mg) plus ledipasvir (90 mg), potent NS5A inhibitor, in a single pill taken once per day. Approved by the FDA for treatment of genotype 1[10], with trials in genotype 3.

**Ombitasvir-Paritaprevir/Ritonavir and dasabuvir (Viekirax):** Oral regimen combining four drugs (12.5-75-250-50 mg). Ombitasvir is a pan- genotypic NS5A inhibitor, paritaprevir inhibits NS3/4A protease, and dasabuvir is a non-nucleoside NS5B polymerase inhibitor. Ritonavir is a potent CYP3A4 enzyme inhibitor that, given with the other drugs, can increase the plasma concentration, mainly of paritaprevir. The FDA approved it in 2014 for genotype 1, but only in combination therapy. The individual use of each drug is not approved[11].

***Future DAA***

Drugs pending commercialization in the near future are combinations of various antivirals.

**MSD (Merck Sharp and Dohme) combo:** Grazoprevir (MK-5172), 100 mg, a second generation protease inhibitor, + Elbasvir (MK-8742), 50 mg, a second generation NS5A inhibitor[12].

**BMS (Bristol-Myers Squibb) combo:** Asunaprevir+daclatasvir+beclabuvir: a combination of daclatasvir, asunaprevir (NS3 protease inhibitor), and beclabuvir (a non-nucleoside NS5B polymerase inhibitor) with activity in genotypes 1, 2, 3, 4 and 5; and variable activity in genotype 6[13].

**SELECTION OF CANDIDATE PATIENTS FOR ANTIVIRAL TREATMENT**

All patients with chronic hepatitis C, whether monoinfected or coinfected with HIV, are candidates for antiviral therapy, both naive and those who have failed to respond to previous treatment, independently of the regimen received.

To select the suitable therapeutic regimen the patients must be classified as naive, or if they have been treated previously, as non-responders or relapsers.

Clinically, it is necessary to evaluate the severity of the liver disease, measuring the degree of fibrosis, using elastography or fibrotest, and in certain cases take a liver biopsy. In cases of cirrhosis, it is necessary to discriminate between compensated and decompensated disease. It is also necessary to identify the presence of extrahepatic manifestations of HCV.

Virologically, it is necessary to know the genotype and its subtype, as well as the viral load, for which the use of sensitive (detection limit of 10-15 IU/mL) and easily available methods is recommended. In some cases it is advisable to determine the IL28B polymorphism or Q80K mutation.

Once the patient has been categorised clinically and virologically, treatment should be prioritised in cases of advanced fibrosis (F2-F4), in patients on the active liver transplant waiting list, liver transplant patients with recurrence of the infection, non-liver transplant patients with HCV hepatitis (independently of the degree of fibrosis), non-responders to triple therapy, or patients with extrahepatic manifestations of HCV. In addition, and independently of the disease status, treatment should also be considered for patients at high risk of transmission or women of child-bearing age. Treatment in patients with mild degrees of fibrosis (F0, F1) can be deferred, though these patients should be assessed individually[14,15].

Interferon-free regimens should be considered the choice.

**TREATMENT IN GENOTYPE 1 PATIENTS**

***Sofosbuvir + Pegylated interferon + Ribavirin***

Efficacy data on the combination of bitherapy with sofosbuvir (SOF) are based on the NEUTRINO registry, which includes naive patients treated with SOF + pegylated interferon (PEG)/ribavirin (RBV) (1000-1200 mg per day) for 12 wk. This regimen obtained SVR12 rates in genotype 1% of 90% (somewhat greater in genotype 1a *vs* genotype 1b), falling to 80% in cirrhotic patients, though this was just a small group (17%)[16]. The secondary effects were those expected with bitherapy.

In naive genotype 1 patients with no contraindication for interferon the regimen SOF+PEG+RBV obtained a SVR of around 90% in the non-cirrhotic and 80% in the cirrhotic patients.

***SOF + RBV***

The results of the phase 2 studies QUANTUM and ELECTRON, with low rates of SVR in genotype 1 patients treated for 12 wk with SOF+RBV, particularly in the retreated patients, show this to be a suboptimal option, even when prolonged for 24 wk[17]. The adverse effects were those associated with the use of ribavirin.

SOF+RBV in genotype 1 is considered a suboptimal therapy.

***SOF + Simeprevir***

The phase 2 study COSMOS included a cohort of patients who were null responders to treatment with interferon and ribavirin with F0-F2 and another cohort of naive and null responder patients with F3-F4 (compensated cirrhosis). They received SOF+ Simeprevir (SIM) +RBV for 12 wk or 24 wk. The rate of SVR12 was above 90%, similar in both groups (mild fibrosis *vs* advanced fibrosis). There were no differences in SVR12 according to the duration of the treatment (12 wk *vs* 24 wk), nor did it change with the addition of RBV, even in F4 patients. Nor were differences found between the naive patients and those treated previously[18]. The presence of the Q80K polymorphism, which is associated with a reduction in the activity of simeprevir in genotype 1a patients when used in combination with PEG and RBV[19], had no impact on the rates of SVR.

The secondary effects were generally mild, mainly headache, fatigue and nauseas. Only 2% presented serious adverse events.

Observational studies provide data from real clinical practice. The TARGET cohort included over 2300 patients grouped in four arms: SOF+PEG+RBV, SOF+RBV, SOF/SIM, and SOF+SIM+RBV. The efficacy of SOF/SIM was very high, around 90%, in both genotype 1a and 1b patients, and similar in cirrhotic and non-cirrhotic patients. The addition of RBV did not increase the rates of SVR[20]. The factor predicting a lower response was failure with previous treatment. The adverse effects were those seen in the clinical trials.

The TRI cohort randomised 1211 patients to receive SOF+PEG+RBV, SOF+RBV, or SOF+SIM+RBV. One third was cirrhotic. A total of 42% received SOF+SIM+RBV with a SVR of 82% (90% per protocol) in genotype 1; 3% discontinued treatment due to adverse effects or lack of treatment adherence. Overall in this study cirrhosis was found to be a predictor of less response, mainly to triple therapy[21].

SOF+SIM for 12 wk in genotype 1 (1a, 1b) showed a SVR of 90%, in both non- cirrhotic patients and in compensated cirrhotic patients (slightly lower), whether or not they were naive or had received previous therapy. The addition of ribavirin or prolonging the treatment did not influence the SVR. It is not advised in Child C and may be suboptimal in cirrhotic patients who have failed to respond to previous treatment. The Q80K mutation has a lower impact on the SVR when SIM is combined with SOF.

***SOF + DCV***

The combination of SOF+DCV was assessed in an open-label phase III trial, which included patients with different genotypes. One naive genotype 1 group, treated for 12 wk with or without RBV, and another genotype 1 group previously treated with triple therapy with protease inhibitors (PI), in whom treatment with SOF+DCV was prolonged to week 24. 98% of the naive patients and the retreated patients had SVR12 with this regimen. The results were similar for genotypes 1a and 1b, and remained unchanged whether or not RBV was added.

The importance of these results concerns the SVR achieved with SOF+DCV at 24 wk in patients who had failed using triple therapy with PI[22]. The most common adverse effects were headache, nausea and fatigue.

SOF and DCV for 12 wk is a good treatment option in patients with genotype 1a/1b, with or without RBV, as well as being a good alternative (24 wk) in patients with failure after triple therapy.

***SOF + LDV***

This combination was analysed in the ION-1 study, which included naive genotype 1 patients, 16% of them cirrhotic, treated with SOF/LDV randomised to 12 or 24 wk, with or without RBV. No statistically significant differences were found in SVR between 12 and 24 wk of treatment (99% *vs* 98%), nor were there significant differences when RBV was added to the treatment[23].

The ION-2 study included patients previously treated with bitherapy or triple therapy with first generation PI, including 20% of cirrhotic patients, treated for 12 and 24 wk, with or without RBV. The results were again similar, with a similar SVR (96%) after 12 and 24 wk of treatment, with or without RBV. Nevertheless, in the group of cirrhotic patients previously treated with PI, the option of SOF+LDV+RBV for 12 wk or SOF+LDV for 24 wk did increase significantly the rate of SVR, as opposed to the option SOF+LDV for 12 wk (99% *vs* 94%)[24].

The ION-3 study, which aimed to evaluate the possibility of shortening treatment, included naive, non-cirrhotic genotype 1 patients randomised to 8 or 12 wk of treatment with SOF/LDV, with or without RBV. The percentage of SVR12 was similar in those treated for 8 and for 12 wk; the addition of RBV provided no extra benefit. However, a subgroup of patients, those with a viral load above 6 million IU/mL, had a greater risk of recurrence if they just received treatment for 8 wk. Cases of resistance to LDV, but not to SOF, were seen but this was not shown to impact on treatment response or the risk of recurrence[25].

Finally, the SOLAR-1 study analysed the efficacy of SOF/LDV in decompensated cirrhotic patients (Child B and C, but with bilirubin < 10 mg/dL, haemoglobin > 10 g/dL and platelets > 30000) who had been excluded from previous studies, treated for 12 and 24 wk, all with RBV. The SVR12 was almost 90% in both groups: Child stages B and C, similar with 12 or 24 wk of treatment[26]. However, there were notable secondary effects and even deaths, mainly due to septic complications.

SOF+LDV obtained SVR rates nearly 100%, but in cirrhotic patients with failure to previous therapy or decompensated cirrhotic patients it is necessary to add RBV if treatment is for 12 wk or else prolong treatment for 24 wk if it is not possible to treat with RBV.

In non-cirrhotic naive patients with a basal viral load less than 6 million IU/mL treatment can be shortened to 8 wk.

***3D Abbvie: Paritaprevir + Ombitasvir + Dasabuvir + Ribavirin***

Phase 3 studies have analysed the results of this combination plus ribavirin in naive non-cirrhotic genotype 1 patients, SAPHIRE I, and previously treated, SAPHIRE II. In both studies the SVR12 was 96%, with no differences between genotype 1a/1b[27].

The phase 3 study TURQUOISE II included compensated cirrhotic genotype 1 patients, both naive and pretreated with this combination from Abbvie plus ribavirin for 12 or 24 wk. The percentages of SVR12 were similar[28].

The impact of RBV on the SVR was analysed in the PEARL study, which showed that the SVR was higher when RBV was added in the cirrhotic genotype 1a and 1b patients. However, RBV had little effect on the SVR in non- cirrhotic genotype 1b patients[29].

Paritaprevir + Ombitasvir + Dasabuvir given for 12 wk is efficient in naive and retreated patients, though it is necessary to add ribavirin in cirrhotic patients and in genotype 1a patients (whether cirrhotic or not). Consideration should be given to prolonging treatment to 24 wk if ribavirin cannot be added in these cases, and always in retreated cirrhotic genotype 1a patients.

***Grazoprevir (MK-5172) + Elbasvir (MK8742)***

Grazoprevir 100 mg per day plus elbasvir 50 mg per day: This MSD combo will soon be available. It was analysed in the c-WORTHY study[30], which examined this combination, with and without RBV, in naive, non-cirrhotic genotype 1 monoinfected and HIV coinfected patients. The genotypes 1a/1b monoinfected patients were randomised to one of three arms: combo plus RBV for 8 weeks, combo plus RBV for 12 wk, and combo without RBV for 12 wk. The 8-week regimen proved insufficient (80% SVR), but treatment for 12 wk achieved 98% SVR, independently of whether RBV was or was not added.

This combo was used in cirrhotic patients and patients with treatment failure, null responders, with and without RBV, for 12 and 18 wk[31]. The results showed that naive cirrhotic patients treated for 12 wk without RBV reached 97% SVR, and the null responders with or without cirrhosis treated for 12 weeks without RBV had a SVR of 98%. Thus, RBV did not change the rates of SVR, nor were there significant changes when prolonging the treatment 18 wk.

MSD combo for 12 wk, SVR of 98% whether genotype 1a/1b, naive or pretreated, cirrhotic or non-cirrhotic. RBV did not change the SVR.

These drugs have also been combined with sofosbuvir in naive patients with and without cirrhosis, as well as assessing the possibility of short-term treatment, 4 or 8 wk, in the C-SWIFT study[32]. Although at some time during the study or after ending it, all the patients were negative for the virus, in those treated for 4 weeks there were many cases of recurrence (19 out of 31). The patients treated for 8 weeks, even the cirrhotic patients, had 94% SVR, with just one recurrence.

***Asunaprevir + Daclatasvir + BMS-791325***

This BMS combo, soon to be commercialised, analysed non-cirrhotic naive and retreated patients in the UNITY-1 study. A SVR of around 90% was achieved, slightly lower in the genotype 1a patients, but similar in both naive and pretreated patients[33]. The cirrhotic patients were analysed in the UNITY-2 study, receiving this combination with or without RBV. In this group of cirrhotic patients RBV increased the rates of SVR in both naive and pretreated patients[34].

The BMS combo obtained a SVR in 90% of cases, but cirrhotic patients require the addition of RBV.

The current recommendations for therapy in patients with genotype 1 HCV are summarised in Tables 1 and 2.

**TREATMENT IN GENOTYPE 2 PATIENTS**

***SOF + PEG + RBV***

The combination of SOF plus pegylated interferon and ribavirin for 12 wk in genotype 2 patients was analysed in the LONESTAR-2 study, a phase II trial that included previously treated patients, even cirrhotic, with a SVR of 96%[35].

***SOF + RBV***

In the FISSION study[36] sofosbuvir was administered in combination with ribavirin for 12 weeks to naive genotype 2 (and 3) patients, analysing the response (compared with standard therapy) according to the degree of fibrosis, although only 20% had cirrhosis. The SVR12 was 91% in the cirrhotic patients and 98% in the non-cirrhotic patients.

Another trial (POSITRON) also included naive patients treated with SOF+RBV, obtaining a SVR of about 90%, in both cirrhotic and non-cirrhotic patients[37].

Previously treated genotype 2 patients were assessed in the phase 3 FUSION study, which also analysed their degree of fibrosis. A response was obtained in 96% of the non-cirrhotic patients treated with SOF+RBV for 12 wk, but inonly 60% of the cirrhotic patients, though this could be increased to 76% when the treatment was prolonged to 16 wk[38].

The VALENCE study included naive and retreated patients and found similar results, with a lower response in the cirrhotic patients[37].

Thus, the only current interferon-free regimen recommended for genotype 2 patients is SOF+RBV for 12 wk, in both naive and pretreated patients, advising it be extended to 16 wk in cirrhotic patients.

In the absence of a contraindication for interferon, SOF+PEG+RBV for 12 wk is a better alternative.

**TREATMENT IN GENOTYPE 3 PATIENTS**

***SOF + RBV + PEG***

The genotype 3 patients retreated with SOF+PEG+RBV for 12 wk, also included in the LONESTAR-2 study, presented a SVR12 of 83%, both the cirrhotic and the non-cirrhotic patients[35]. This percentage increased if the patient was naive. If there is no contraindication to interferon, this is one of the best alternatives in genotype 3 patients.

***SOF + RBV***

The analysis in the FISSION study of the genotype 3 patients, treated with SOF+RBV for 12 weeks, showed low rates of SVR12, around 60% in the non- cirrhotic and 30% in the cirrhotic patients[7,16].

Likewise the genotype 3 patients in the FUSION study showed a low SVR with SOF+RBV for 12 wk, though a 60% response rate was achieved if they were treated for 16 weeks, both cirrhotic and non-cirrhotic patients.

However, the genotype 3 patients in the VALENCE study (naive and retreated), who received SOF+RBV for 24 wk, attained a SVR of 94% in the naive patients (cirrhotic and non-cirrhotic) and 60% in the retreated cirrhotic patients[39].

In general terms SOF+RBV for 24 wk may be an option in genotype 3 patients, except in retreated cirrhotic patients where it is considered suboptimal.

***SOF + DCV***

The ALLY-3 study included naive and retreated genotype 3 patients who received SOF plus DCV for 12 wk. The non-cirrhotic patients had a SVR12 of 97% if they were naive and 94% if they were retreated. However, the cirrhotic patients had a suboptimal response, 58% SVR in naive and 69% in retreated patients[40].

SOF+DCV is considered suboptimal in cirrhotic genotype 3 patients.

***SOF + LDV***

The ELECTRON-2 trail[41] randomised naive genotype 3 patients to receive SOF+LDV or SOF+LDV+RBV. Only 15% had cirrhosis. In the group treated with RBV the SVR12 was 100%, versus 64% in the arm without RBV. Later, previously treated patients were included, even if they were cirrhotic, resulting in 89% SVR12 with SOF+LDV+RBV. Nevertheless, in vitro, LDV has a limited activity in genotype 3 patients[42], so that, although it can be considered a possible alternative, further studies and data are necessary before it can be recommended as a first choice option.

If treatment is with SOF+LDV it is advisable to add RBV.

The treatment options for genotypes 2 and 3 patients are summarised in Table 3.

**TREATMENT IN GENOTYPES 4, 5 and 6 PATIENTS**

The lower frequency of these genotypes means their analysis in phase 2 and 3 trials is skewed by the reduced number of patients.

***SOF + PEG + RBV***

The phase 2 ATOMIC study, although designed to analyse genotype 1 patients, also included a small group of genotypes 4 and 6 patients treated for 24 wk. A SVR12 of 82% was obtained in the genotype 4 patients and 100% in the genotype 6 patients[43]. The NEUTRINO trial[16] also included a few genotypes 4, 5 and 6 patients, with a SVR12 of 96-100%.

***SOF + LDV***

A small group of naive and retreated genotype 4 patients was evaluated in the SYNERGY study. Those treated with SOF+LDV had a SVR of 95% (33% were cirrhotic)[44].

Around 20 genotype 6 patients were included in the ELECTRON-2 study[41], most retreated and 8% cirrhotic, with a SVR of 96%.

Although this combination shows in vitro efficacy in genotype 5 patients, no study yet exists to support its recommendation.

***SOF + RBV***

The Egyptian ancestry study grouped genotype 4 patients, 50% retreated and 17% cirrhotic, treated with SOF+RBV for 12 or 24 wk. The non-cirrhotic patients treated for 12 wk had a similar SVR to those treated for 4 wk (around 90%), but the cirrhotic patients treated for just 12 wk had a worse response[45].

***Paritaprevir + ombitasvir***

Use of this combination, with or without RBV, in genotype 4 patients was analysed in the PEARL-1 study, which did not include any cirrhotic patients. The SVR12 was 95% in the naive patients and 100% in the retreated patients, provided RBV was added; otherwise the response was lower in both groups[29]. The treatment options recommended for genotypes 4, 5 and 6 patients are summarised in Table 4.

**TREATMENT IN SPECIAL POPULATIONS**

***Patients on the active liver transplant waiting list***

Patients on the active liver transplant waiting list are a difficult group to treat, particularly those who have advanced cirrhosis. Even so, antiviral therapy is indicated in all wait list patients, as it can prevent the recurrence of post-transplant disease, a situation associated with worse graft and patient survival. Negativization of the HCV-RNA before transplantation reduces the risk of recurrence[46].

Except for those patients on the waiting list due to hepatocarcinoma, with good liver function, in whom interferon-based therapy could have some indication. Interferon-free regimens are the treatment of choice

The combination of SOF+RBV for 48 wk has been evaluated in patients on the wait list due to hepatocarcinoma, the vast majority with Child A status[47]. At the time of transplantation 92% had a negative viral load, with 69% having a SVR12. The main predictor of SVR12 was the duration of an undetectable viral load prior to transplantation. Only one patient whose HCV-RNA was negative for 28 d before transplantation experienced recurrence.

However, most patients on the liver transplant waiting list have advanced disease, and the option of SOF+RBV in these patients has been shown to be suboptimal. The recommendations referring to the general population should be applied to these patients, considering that data are available related to real clinical practice using SOF+SIM[20,21] and that SOF + LDV has been used in decompensated cirrhotic patients[26], whilst few data are available concerning the use of DAA in patients with Child C or MELD > 20.

***Patients with post-transplant relapse***

Recurrence of HCV reduces both graft and patient survival. Historically, treatment of recurrence was based on interferon strategies, with low response rates and a high risk of adverse events and/or severe rejection[48]. However, the appearance of new DAA has changed the panorama. If treatment is not possible before transplantation, it is recommended in all patients who experience post- transplant recurrence.

Again the recommendations can be extrapolated from studies in the general population. Possible interactions between DAA and immunosuppressive drugs should be considered. Simeprevir can interact with cyclosporine and paritaprevir with cyclosporine and tacrolimus, but it is not generally necessary to adjust the dose of any of these drugs[49]. The combination of SOF+RBV for 24 wk can give a SVR of 70%. Although there were no episodes of rejection, side effects associated with ribavirin were noted[50].

Data are available from real clinical practice of SOF+SIM for 12 wk, with or without ribavirin (in genotype 1) with SVR12 above 90%, very good tolerance and few side effects, though there was one death related with possible pulmonary toxicity. Only a minimum adjustment of immunosuppressants was necessary. The addition of RBV had no impact on the SVR, though the degree of fibrosis did have an effect, with a fall in the SVR in patients with F4[51].

The CORAL-1 study included patients with post-transplant recurrence of HCV (genotype 1a) treated with the Abbvie combo plus ribavirin for 12 and 24 wk[52]. An SVR of 97% was obtained in those treated for 12 and 24 wk, though again an advanced degree of fibrosis reduced this percentage.

***Patients with chronic kidney failure on haemodialysis***

Patients with moderate chronic kidney failure (CrCl 30-80 mL/min) can follow the general recommendations, bearing in mind that no dose adjustment is necessary for sofosbuvir, simprevir, ledipasvir or the Abbvie combo[53]. However, no efficacy or safety data are available for patients with a CrCl < 30 mL/min.

Patients on haemodialysis have a high prevalence of HCV infection, which suggests a possible nosocomial transmission, with a negative impact on quality of life and an increase in mortality as compared with haemodialysis patients without HCV[54]. Although these patients are considered candidates for antiviral therapy, particularly if they are scheduled for kidney transplantation, they should receive treatment free of interferon and ribavirin, though no safety data are available with the use of DAA.

***Patients with extrahepatic manifestations of HCV***

Cryoglobulinemic vasculitis is an indication for antiviral therapy. As interferon, although it induces remission, can occasionally exacerbate the symptoms, interferon-free regimens are recommended, using new DAA in conjunction with the usual measures, like plasmapheresis or immunosuppressors[55]. Glomerular disease due to deposits of immunocomplexes also benefits from antiviral therapy, though so far the previous therapies have failed to completely revert the disease[56]. The new DAA could have a better repercussion on kidney disease given the high SVR, but no data are yet available.

The prevalence of type 2 diabetes is increasing in patients with HCV, due to complex and not well understood mechanisms, but in relation to an increase in insulin resistance[57]. In fact, virus negativisation after antiviral treatment is associated with an improvement in markers of insulin resistance and a lower incidence of diabetes, as well as a reduction in diabetic nephropathy and cardiovascular complications[58]. Accordingly, the high effectiveness of the new DAA can again provide great benefits.

**IMPACT OF THE NEW DAA ON THE NATURAL HISTORY OF HCV DISEASE**

The aim of treatment with the new antivirals, as currently practised, is to reduce the complications related with the disease, such as the evolution to cirrhosis and its decompensations, and/or the appearance of hepatocarcinoma. In addition, data exist concerning an improved liver function after treatment with DAA, with a reduction in the Child and the MELD scores, and even the possibility of taking patients off the active liver transplant waiting list[26].

The impact of the use of DAA in patients with established hepatocarcinoma, however, is not yet clear. Accordingly, their indication should be individualized, bearing in mind the characteristics of the patient, their clinical situation and the particular candidate options available for treatment of the hepatocarcinoma. Nevertheless, strategic plans should be established to detect HCV carriers, making an early diagnosis and treatment.

**CONCLUSION**

The appearance of direct acting antiviral drugs has radically changed the management of patients with chronic hepatitis C. The high rates of SVR are related with the reduction of the progression to cirrhosis and a lower incidence of complications with established cirrhosis. In the setting of liver transplantation, treatment with DAA results in the great majority of patients having a negative viral load at the time of transplantation, thus reducing the risk of recurrence; and if this does occur it can be treated quickly, safely and effectively.

Future strategies to quickly detect, diagnose and treat HCV carriers could achieve the eradication of the disease.

**REFERENCES**

1 **Gower E**, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. *J Hepatol* 2014; **61**: S45-S57 [PMID: 25086286 DOI: 10.1016/j.jhep.2014.07.027]

2 **Jacobson IM**, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, Marcellin P, Muir AJ, Ferenci P, Flisiak R, George J, Rizzetto M, Shouval D, Sola R, Terg RA, Yoshida EM, Adda N, Bengtsson L, Sankoh AJ, Kieffer TL, George S, Kauffman RS, Zeuzem S. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011; **364**: 2405-2416 [PMID: 21696307 DOI: 10.1056/NEJMoa1012912]

3 **Poordad F**, McCone J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, Jacobson IM, Reddy KR, Goodman ZD, Boparai N, DiNubile MJ, Sniukiene V, Brass CA, Albrecht JK, Bronowicki JP. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364**: 1195-1206 [PMID: 21449783 DOI: 10.1056/NEJMoa1010494]

4 **Hézode C**, Fontaine H, Dorival C, Zoulim F, Larrey D, Canva V, De Ledinghen V, Poynard T, Samuel D, Bourliere M, Alric L, Raabe JJ, Zarski JP, Marcellin P, Riachi G, Bernard PH, Loustaud-Ratti V, Chazouilleres O, Abergel A, Guyader D, Metivier S, Tran A, Di Martino V, Causse X, Dao T, Lucidarme D, Portal I, Cacoub P, Gournay J, Grando-Lemaire V, Hillon P, Attali P, Fontanges T, Rosa I, Petrov-Sanchez V, Barthe Y, Pawlotsky JM, Pol S, Carrat F, Bronowicki JP. Effectiveness of telaprevir or boceprevir in treatment-experienced patients with HCV genotype 1 infection and cirrhosis. *Gastroenterology* 2014; **147**: 132-142.e4 [PMID: 24704719 DOI: 10.1053/j.gastro.2014.03.051]

5 **Liang TJ**, Ghany MG. Current and future therapies for hepatitis C virus infection. *N Engl J Med* 2013; **368**: 1907-1917 [PMID: 23675659 DOI: 10.1056/NEJMra1213651]

6 **Belperio PS**, Backus LI, Ross D, Neuhauser MM, Mole LA. A population approach to disease management: hepatitis C direct-acting antiviral use in a large health care system. *J Manag Care Spec Pharm* 2014; **20**: 533-540 [PMID: 24856591]

7 **Gane EJ**, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, Hindes RG, Berrey MM. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med* 2013; **368**: 34-44 [PMID: 23281974 DOI: 10.1056/NEJMoa1208953]

8 **Manns M**, Marcellin P, Poordad F, de Araujo E.S. F, Buti M, Horsmans Y, Janczewska E, Villamil F, Scott J, Peeters M, Lenz O, Ouwerkerk-Mahadevan S, De La Rosa G, Kalmeijer R, Sinha R, Beumont-Mauviel M. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial*. Lancet* 2014;**2**: 414-426 [PMID: 24907224 DOI: 10.1016/S0140-6736(14)60538-9]

9 **Amano M**, Ishikawa H. [Pharmacological properties and clinical efficacy of daclatasvir (Daklinza®) and asunaprevir (Sunvepra®)]. *Nihon Yakurigaku Zasshi* 2015; **145**: 152-162 [PMID: 25765498 DOI: 10.1254/fpj.145.152]

10 **Keating GM**. Ledipasvir/Sofosbuvir: a review of its use in chronic hepatitis C. *Drugs* 2015; **75**: 675-685 [PMID: 25837989 DOI: 10.1007/s40265-015-0381-2]

11 **Andreone P**, Colombo MG, Enejosa JV, Koksal I, Ferenci P, Maieron A, Müllhaupt B, Horsmans Y, Weiland O, Reesink HW, Rodrigues L, Hu YB, Podsadecki T, Bernstein B. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. *Gastroenterology* 2014; **147**: 359-365.e1 [PMID: 24818763 DOI: 10.1053/j.gastro2014.04.045]

12 **Zeuzem S**, Ghalib R, Reddy KR, Pockros PJ, Ari ZB, Zhao Y, Brown DD, Wan S, DiNubile MJ, Nguyen BY, Robertson MN, Wahl J, Barr E, Butterton JR. Grazoprevir-Elbasvir Combination Therapy for Treatment-Naive Cirrhotic and Noncirrhotic Patients With Chronic Hepatitis C Virus Genotype 1, 4, or 6 Infection: A Randomized Trial. *Ann Intern Med* 2015; **163**: 1-13 [PMID: 25909356 DOI: 10.7326/M15-0785]

13 **Hassanein T**, Sims KD, Bennett M, Gitlin N, Lawitz E, Nguyen T, Webster L, Younossi Z, Schwartz H, Thuluvath PJ, Zhou H, Rege B, McPhee F, Zhou N, Wind-Rotolo M, Chung E, Griffies A, Grasela DM, Gardiner DF. A randomized trial of daclatasvir in combination with asunaprevir and beclabuvir in patients with chronic hepatitis C virus genotype 4 infection. *J Hepatol* 2015; **62**: 1204-1206 [PMID: 25559328 DOI: 10.116/j.jhep2014.12.025]

14 **European association for the study of the liver.** EASL recommendation on treatment of hepatitis C 2015. Clinical practice guidelines: Management of hepatitis C virus infection. *J Hepatol* 2015; In press [DOI: 10.1016/j.jhep.2015.03.025]

15 **AASLD and Infectious Diseases society of América (IDSA).** Uptodate to recommendations for testing, managing and treating hepatitis C: management of acute HCV infection.

# 16 Lawitz E, Lalezari JP, Hassanein T, Kowdley HV, Poordad FF, Sheikh AM, Afdhak HN, Bernstein DE, Dejesus E, Freillich B, Nelson DR, Dietrich DT, Jacobson IM, Jensen D, Abrams GA, Darling JM, Rodriguez-Torres M, Reddy KR, Sulkowski MS, Bzowej NH, Hyland RH, Mo H, Lin M, Mader M, Hindes R, Albanis E, Symonds WT, Berrey MM, Miur A. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. *Lancet Infect Dis* 2013; 13: 401-408 [PMID: 23499158 DOI: 10.1016/S1473-3099(13)70033-1]

17 **Mariño Z**, van Bömmel F, Forns X, Berg T. New concepts of sofosbuvir-based treatment regimens in patients with hepatitis C. *Gut* 2014; **63**: 207-215 [PMID: 24253934 DOI: 10.1136/gutjnl-2013-305771]

18 **Lawitz E**, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, DeJesus E, Pearlman B, Rabinovitz M, Gitlin N, Lim JK, Pockros PJ, Scott JD, Fevery B, Lambrecht T, Ouwerkerk-Mahadevan S, Callewaert K, Symonds WT, Picchio G, Lindsay KL, Beumont M, Jacobson IM. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. *Lancet* 2014; **384**: 1756-1765 [PMID: 25078309 DOI: 10.1016/S0140-6736(14)61036-9]

19 **Jacobson IM**, Dore GJ, Foster GR, Fried MW, Radu M, Rafalsky VV, Moroz L, Craxi A, Peeters M, Lenz O, Ouwerkerk-Mahadevan S, De La Rosa G, Kalmeijer R, Scott J, Sinha R, Beumont-Mauviel M. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet* 2014; **384**: 403-413 [PMID: 24907225 DOI: 10.1016/S0140-6736(14)60494-3]

20 **Jensen DM,** Oleary J, Pcokros P, Sherman K, Kwo P, Mailliard M, Kowdley K, Muir A, Dickson R, Ramani A, Manns M, Lok A, Akushevich L, Nelson D, Fried M. Safety and efficacy of Sofosbuvir-containing regimens for hepatitis C: Real-world experience in a diverse, longitudinal observational cohort. In: Abstract AASLD 2014

21 **Dieterich D,** Bacon B, Flamm S, Kowdley K, Milligan S, Tsai N, Younossi Z, Lawitz E. Evaluation of sofosbuvir and simprevir-based regimens in the TRIO network-Academic and community treatment of a real-world, heterogeneous population. In: Abstract AASLD 2014

22 **Sulkowski MS**, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, Lawitz E, Lok AS, Hinestrosa F, Thuluvath PJ, Schwartz H, Nelson DR, Everson GT, Eley T, Wind-Rotolo M, Huang SP, Gao M, Hernandez D, McPhee F, Sherman D, Hindes R, Symonds W, Pasquinelli C, Grasela DM. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *N Engl J Med* 2014; **370**: 211-221 [PMID: 24428467 DOI: 10.1056/NEJMoa1306218]

23 **Afdhal N**, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, Romero-Gomez M, Zarski JP, Agarwal K, Buggisch P, Foster GR, Bräu N, Buti M, Jacobson IM, Subramanian GM, Ding X, Mo H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Mangia A, Marcellin P. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014; **370**: 1889-1898 [PMID: 24725239 DOI: 10.1056/NEJMoa1402454]

24 **Bhardwaj A**, Kaur J, Wuest F, Knaus EE. Do nitric oxide-releasing drugs offer a potentially new paradigm for the management of cardiovascular risks in diabetes? *Expert Rev Cardiovasc Ther* 2014; **12**: 533-536 [PMID: 24725228 DOI: 10.1056/NEJMoa1316366]

25 **Kowdley KV**, Lawitz E, Poordad F, Cohen DE, Nelson DR, Zeuzem S, Everson GT, Kwo P, Foster GR, Sulkowski MS, Xie W, Pilot-Matias T, Liossis G, Larsen L, Khatri A, Podsadecki T, Bernstein B. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. *N Engl J Med* 2014; **370**: 222-232 [PMID: 24428468 DOI: 10.1056/NEJMoa1306227]

26 **Flamm SL,** Everson GT, Charlton. Ledipasvir/sofosbuvir with ribavirin for the treatment of HCV in patients with descomensated cirrosis: preliminar results of a prospective, multicenter study. In: Abstract AASLD 2014

27 **Feld JJ**, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, Weiland O, Aguilar H, Xiong J, Pilot-Matias T, DaSilva-Tillmann B, Larsen L, Podsadecki T, Bernstein B. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014; **370**: 1594-1603 [PMID: 24720703 DOI: 10.1056/NEJMoa1315722]

28 **Poordad F**, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, Shiffman ML, Wedemeyer H, Berg T, Yoshida EM, Forns X, Lovell SS, Da Silva-Tillmann B, Collins CA, Campbell AL, Podsadecki T, Bernstein B. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med* 2014; **370**: 1973-1982 [PMID: 24725237 DOI: 10.1056/NEJMoa1402869]

29 **Ferenci P**, Bernstein D, Lalezari J, Cohen D, Luo Y, Cooper C, Tam E, Marinho RT, Tsai N, Nyberg A, Box TD, Younes Z, Enayati P, Green S, Baruch Y, Bhandari BR, Caruntu FA, Sepe T, Chulanov V, Janczewska E, Rizzardini G, Gervain J, Planas R, Moreno C, Hassanein T, Xie W, King M, Podsadecki T, Reddy KR. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. *N Engl J Med* 2014; **370**: 1983-1992 [PMID: 24795200 DOI: 10.1056/NEJMoa1402338]

30 **Sulkowski M**, Hezode C, Gerstoft J, Vierling JM, Mallolas J, Pol S, Kugelmas M, Murillo A, Weis N, Nahass R, Shibolet O, Serfaty L, Bourliere M, DeJesus E, Zuckerman E, Dutko F, Shaughnessy M, Hwang P, Howe AY, Wahl J, Robertson M, Barr E, Haber B. Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in patients with hepatitis C virus genotype 1 mono-infection and HIV/hepatitis C virus co-infection (C-WORTHY): a randomised, open-label phase 2 trial. *Lancet* 2015; **385**: 1087-1097 [PMID: 25467560 DOI: 10.1016/S0140-6736(14)61793-1]

31 **Lawitz E,** Gane E, Pearlman B, Tam E, Ghesquiere W, Guyader D, Alric L, Bronowicki JP, Lester L, Sievert W, Ghalib R, Balart L, Sund F, Lagging M, Dutko F, Shaughnessy M, Hwang P, Howe AY, Wahl J, Robertson M, Barr E, Haber B. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. *Lancet* 2015; **385**: 1075-1086 [PMID: 25467591 DOI: 10.1016/S0140-6736(14)61795-5]

32 **Lawitz E,** Poordad F, Gutierrez JA, Evans B, Hwang P, Howe A, Feng HP, Robertson M, Wahl J, Barr E, Hber B. C-SWITZ: Grazoprevir (MK-5172) Elbasvir (MK-8742) Sofosbuvir in treatment-naive patients with hepatitis C virus genotype 1 infection, with or without cirrhosis, for duration4, 6, or 8 weeks (interim results). In: abstract AASLD 2014

33 **Poordad F,** Sievert W, Mollison L, Brau N, Levin J, Sepe T, Lee S, Boyer N, Bronowicki JP, Jacobson IM, Boparai N, Hughes E, Swenson ES, Yin PD, on behalf of the UNITY-1 study team. All-oral, fixed-dosed combination therapy with daclatasvir/asunaprevir/beclabuvie for non-cirrhotic patients with chronic HCV genotype 1 infection: UNITY-1 phase 3 SVR 12 results. In: Abstract AASLD 2014

34 **Poordad F,** Lalezari J, Everson GJ, Dore GJ, Kwo P, Hezode C, Pckros PJ, Tran A, Ramji A, Yang R, Hughes EA, Swenson ES, Yin PD, on behalf of the UNITY-2 study Team. All-oral fixed dose combination therapy with daclatasvir/asunaprevir/Beclabuvir, Ribavirin, for patients with chronic HCV genotype 1 infection and compensated cirrhosis: UNITY-2 phase 3 SVR12 results. In: Abstract AASLD 2014

35 **Lawitz E**, Poordad F, Brainard DM, Hyland RH, An D, Symonds WT, McHutchison JG, Membreno FE. Sofosbuvir in combination with PegIFN and ribavirin dor 12 weeks provides high SVR rates in HCV-Infected getype 2 or 3 treatment.-experienced patients with or without compensated cirrhosis: results from the LONESTAR-2 study. In: abstract AASLD 2014

36 **Lawitz E**, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, Schultz M, Davis MN, Kayali Z, Reddy KR, Jacobson IM, Kowdley KV, Nyberg L, Subramanian GM, Hyland RH, Arterburn S, Jiang D, McNally J, Brainard D, Symonds WT, McHutchison JG, Sheikh AM, Younossi Z, Gane EJ. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013; **368**: 1878-1887 [PMID: 23607594 DOI: 10.1056/NEJMoa1214853]

37 **Bourlière M**, Benali S, Ansaldi C, Le Folgoc G, Riso A, Lecomte L. Optimal therapy of genotype-2 chronic hepatitis C: what's new? *Liver Int* 2015; **35** Suppl 1: 21-26 [PMID: 25529084 DOI: 10.1111/liv.12711]

38 **Jacobson IM**, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, Shiffman ML, Lawitz E, Everson G, Bennett M, Schiff E, Al-Assi MT, Subramanian GM, An D, Lin M, McNally J, Brainard D, Symonds WT, McHutchison JG, Patel K, Feld J, Pianko S, Nelson DR. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med* 2013; **368**: 1867-1877 [PMID: 23607593 DOI: 10.1056/NEJMoa1214854]

39 **Zeuzem S**, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, Illeperuma A, Svarovskaia E, Brainard DM, Symonds WT, Subramanian GM, McHutchison JG, Weiland O, Reesink HW, Ferenci P, Hézode C, Esteban R. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med* 2014; **370**: 1993-2001 [PMID: 24795201 DOI: 10.1056/NEJMoa1316145]

40 **Nelson DR**, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, Freilich BF, Younes ZH, Harlan W, Ghalib R, Oguchi G, Thuluvath PJ, Ortiz-Lasanta G, Rabinovitz M, Bernstein D, Bennett M, Hawkins T, Ravendhran N, Sheikh AM, Varunok P, Kowdley KV, Hennicken D, McPhee F, Rana K, Hughes EA. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. *Hepatology* 2015; **61**: 1127-1135 [PMID: 25614962 DOI: 10.1002/hep.27726]

41 **Gane E,** hilando RH, An Di, Pang PS, Symonds WT, McHutchinson, Stedman CA. Ledipasvis/sofosbuvir fixed-dose combination is safe and effective in difficult-to-treat populations including GT 3 patients, descompesated GT1 patients, and GT 1 patients with prior sofosbuvir experience. In: abstract EASL 2013

42 **Gao M**. Antiviral activity and resistance of HCV NS5A replication complex inhibitors. *Curr Opin Virol* 2013; **3**: 514-520 [PMID: 23896281 DOI: 10.1016/j.coviro.2013.06.014]

43 **Kowdley KV**, Lawitz E, Crespo I, Hassanein T, Davis MN, DeMicco M, Bernstein DE, Afdhal N, Vierling JM, Gordon SC, Anderson JK, Hyland RH, Dvory-Sobol H, An D, Hindes RG, Albanis E, Symonds WT, Berrey MM, Nelson DR, Jacobson IM. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial. *Lancet* 2013; **381**: 2100-2107 [PMID: 23499440 DOI: 10.1016/S0140-6736(13)60247-0]

44 **Kapoor R,** Kohli A, Sidhartahan S, Sims Z, Pertersen T, Osinusi A, Nelson A, Silk R, Kotb C, Sugarman K, Lam BP, Pang PS, Subramanian M, McHutchison JG, Masur H, Kottilil S, Rustgi VK. Treatment of hepatitis C genotype 4 with ledipasvir and sofosbuvir for 12 weeks: results of the SYNERGY trial. In: abstract AASLD 2014.

45 **Ruane PJ**, Ain D, Stryker R, Meshrekey R, Soliman M, Wolfe PR, Riad J, Mikhail S, Kersey K, Jiang D, Massetto B, Doehle B, Kirby BJ, Knox SJ, McHutchison JG, Symonds WT. Sofosbuvir plus ribavirin for the treatment of chronic genotype 4 hepatitis C virus infection in patients of Egyptian ancestry. *J Hepatol* 2015; **62**: 1040-1046 [PMID: 25450208 DOI: 10.1016/j.jhep.2014.10.044]

46 **Forns X**, García-Retortillo M, Serrano T, Feliu A, Suarez F, de la Mata M, García-Valdecasas JC, Navasa M, Rimola A, Rodés J. Antiviral therapy of patients with decompensated cirrhosis to prevent recurrence of hepatitis C after liver transplantation. *J Hepatol* 2003; **39**: 389-396 [PMID: 12927925 DOI: 10.1016/S0168-8278(03)00310-6]

47 **Curry MP**, Forns X, Chung RT, Terrault NA, Brown R, Fenkel JM, Gordon F, O'Leary J, Kuo A, Schiano T, Everson G, Schiff E, Befeler A, Gane E, Saab S, McHutchison JG, Subramanian GM, Symonds WT, Denning J, McNair L, Arterburn S, Svarovskaia E, Moonka D, Afdhal N. Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: an open-label study. *Gastroenterology* 2015; **148**: 100-107.e1 [PMID: 25261839 DOI: 10.1053/j.gastro.2014.09.023]

48 **Jiménez-Pérez M**, González-Grande R, Rando-Muñoz FJ. Management of recurrent hepatitis C virus after liver transplantation. *World J Gastroenterol* 2014; **20**: 16409-16417 [PMID: 25469009 DOI: 10.3748/wjg.v20.i44.16409]

49 **Burgess S**, Partovi N, Yoshida EM, Erb SR, Azalgara VM, Hussaini T. Drug Interactions With Direct-Acting Antivirals for Hepatitis C: Implications for HIV and Transplant Patients. *Ann Pharmacother* 2015; **49**: 674-687 [PMID: 25770114 DOI: 1060028015576180]

50 **Charlton M**, Gane E, Manns MP, Brown RS, Curry MP, Kwo PY, Fontana RJ, Gilroy R, Teperman L, Muir AJ, McHutchison JG, Symonds WT, Brainard D, Kirby B, Dvory-Sobol H, Denning J, Arterburn S, Samuel D, Forns X, Terrault NA. Sofosbuvir and ribavirin for treatment of compensated recurrent hepatitis C virus infection after liver transplantation. *Gastroenterology* 2015; **148**: 108-117 [PMID: 25304641 DOI: 10.1053/j.gastro.2014.10.001]

51 **Pungpapong S**, Aqel B, Leise M, Werner KT, Murphy JL, Henry TM, Ryland K, Chervenak AE, Watt KD, Vargas HE, Keaveny AP. Multicenter experience using simeprevir and sofosbuvir with or without ribavirin to treat hepatitis C genotype 1 after liver transplant. *Hepatology* 2015; **61**: 1880-1886 [PMID: 25722203 DOI: 10.1002/hep.27770]

52 **Kwo PY**, Mantry PS, Coakley E, Te HS, Vargas HE, Brown R, Gordon F, Levitsky J, Terrault NA, Burton JR, Xie W, Setze C, Badri P, Pilot-Matias T, Vilchez RA, Forns X. An interferon-free antiviral regimen for HCV after liver transplantation. *N Engl J Med* 2014; **371**: 2375-2382 [PMID: 25386767 DOI: 10.1056/NEJMoa1408921]

53 **Bunchorntavakul C**, Maneerattanaporn M, Chavalitdhamrong D. Management of patients with hepatitis C infection and renal disease. *World J Hepatol* 2015; **7**: 213-225 [PMID: 25729476 DOI: 10.4254/wjh.v7.i2.213]

54 **Fabrizi F**, Takkouche B, Lunghi G, Dixit V, Messa P, Martin P. The impact of hepatitis C virus infection on survival in dialysis patients: meta-analysis of observational studies. *J Viral Hepat* 2007; **14**: 697-703 [PMID: 17875004]

55 **Saadoun D**, Resche Rigon M, Thibault V, Longuet M, Pol S, Blanc F, Pialoux G, Karras A, Bazin-Karra D, Cazorla C, Vittecoq D, Musset L, Decaux O, Ziza JM, Lambotte O, Cacoub P. Peg-IFNα/ribavirin/protease inhibitor combination in hepatitis C virus associated mixed cryoglobulinemia vasculitis: results at week 24. *Ann Rheum Dis* 2014; **73**: 831-837 [PMID: 23606708 DOI: 10.1136/annrheumdis-2012-202770]

56 **Johnson RJ**, Gretch DR, Couser WG, Alpers CE, Wilson J, Chung M, Hart J, Willson R. Hepatitis C virus-associated glomerulonephritis. Effect of alpha-interferon therapy. *Kidney Int* 1994; **46**: 1700-1704 [PMID: 7535369]

57 **González-Grande R,** Jiménez-Pérez M, Sáez-Gómez AB, Rodrigo-López JM. Metabolic syndrome after liver transplantation. In: Abdeldayem H, Allam N, Liver transplantation Technical issues and complications. Croatia: Ed InTech.

58 **Hsu YC**, Lin JT, Ho HJ, Kao YH, Huang YT, Hsiao NW, Wu MS, Liu YY, Wu CY. Antiviral treatment for hepatitis C virus infection is associated with improved renal and cardiovascular outcomes in diabetic patients. *Hepatology* 2014; **59**: 1293-1302 [PMID: 24122848 DOI: 10.1002/hep.26892]

**P-Reviewer:** Sims OT **S-Editor:** Qi Y **L-Editor: E-Editor:**

**Table 1 Recommendations for therapy in patients with genotype 1a**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Patient characterization** | **Recommended** | **Duration (wk)** | **Scientific evidence** | **Real-world evidence** |
| Genotype 1a naive Noncirrhotic | SOF+LDV  SOF+LDV  (CV < 6 mill UI/ml) | 12  8 | ION-1  ION-3 |  |
| OBV+*PTVR+DSV+RBV* | 12 | SAPHIRE I PEARL |  |
| SOF+SIM | 12 | COSMOS | TARGET TRIO |
| *SOF+DCV* | *12* |  |  |
| SOF+PEG+RBV | 12 | NEUTRINO |  |
| Genotype 1a  NAIVE CIRRHOTIC | SOF+LDV | 12 | ION-1 |  |
| OBV+*PTVR+DSV*+RBV | 12 | TURQUOISE-II PEARL |  |
| SOF+SIM | 12 | COSMOS |  |
| SOF+DCV | 12 |  |  |
| SOF+PEG+RBV | 12 | NEUTRINO |  |
| Genotype 1a retretated noncirrhotic | SOF+LDV | 12 | ION-2 |  |
| OBV+*PTVR+DSV+RBV* | 12 | SAPHIRE-II |  |
| SOF+SIM | 12 | COSMOS |  |
| *SOF+DCV* | *12/24* |  |  |
| Genotipo 1a Retreated cirrhotic | SOF+LDV+RBV | 12 | ION-2 |  |
| SOF+LDV | 24 | ION-2 |  |
| OBV+*PTVR+DSV+RBV* | 12/24 | TURQUOISE-II PEARL |  |
| SOF+SIM | 12 | COSMOS |  |
| *SOF+DVC* | *24* |  |  |

**Table 2 Recommendations for therapy in patients with genotype 1b**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Patient characterization** | **Recommended** | **Duration** | **Scientific evidence** | **Real-world evidence** |
| Genotype 1b naive noncirrhotic | SOF+LDV  SOF+LDV  (CV < 6 mill UI/ml) | 12  8 | ION-1  ION-3 |  |
| OBV+*PTVR+DSV* | 12 | SAPHIRE I PEARL |  |
| SOF+SIM | 12 | COSMOS | TARGET TRIO |
| *SOF+DCV* | *12* |  |  |
| SOF+PEG+RBV | 12 | NEUTRINO |  |
| Genotype 1b  naive cirrhotic | SOF+LDV | 12 | ION-1 |  |
| OBV+*PTVR+DSV*+RBV | 12 | TURQUOISE-II PEARL |  |
| SOF+SIM | 12 | COSMOS |  |
| SOF+DCV | 12 |  |  |
| SOF+PEG+RBV | 12 | NEUTRINO |  |
| Genotype 1b retreated noncirrhotic | SOF+LDV | 12 | ION-2 |  |
| OBV+*PTVR+DSV* | 12 | SAPHIRE-II |  |
| SOF+SIM | 12 | COSMOS |  |
| *SOF+DCV* | *12/24* |  |  |
| genotype 1b retreated cirrhotic | SOF+LDV**+**RBV | 12 | ION-2 |  |
| SOF+LDV | 24 | ION-2 |  |
| OBV+*PTVR+DSV****+RBV*** | 12 | TURQUOISE-II PEARL |  |
| SOF+SIM | 12 | COSMOS |  |
| *SOF+DVC* | *24* |  |  |

**Table 3 Recommedation for therapy in patients with genotypes 2 and 3**

|  |  |  |  |
| --- | --- | --- | --- |
| **Patient characterization** | **Recommended** | **Duration (wk)** | **Scientific evidence** |
| Genotype 2 naive noncirrhotic/Cirrhotic | SOF+RBV | 12 | Fission positron |
| SOF+PEG+RBV | 12 | Lonestar-2 |
| Genotype 2  Retretated NONCIRRHOTIC | SOF+RBV | 12 | Fussion valence |
| SOF+PEG+RBV | 12 | Lonestar-2 |
| Genotype 2  Retreated cirrhotic | SOF+PEG+RBV | 12 | Lonestar-2 |
| SOF+RBV | 16 | Fussion valence |
| Genotype 3 naive and retreated noncirrhotic/ cirrhotic | SOF+RBV | 24 | Valence |
| SOF+PEG+RBV | 12 | Lonestar-2 |
| SOF+LDV+RBV | 12 | Electron-2 |
| SOF+DVC  (NO EN CIRRÓTICOS) | 12 | Ally-3 |

**Table 4 Recommendations for therapy in patients with genotypes 4, 5 and 6**

|  |  |  |  |
| --- | --- | --- | --- |
| **Patient characterization** | **Recommended** | **Duration (wk)** | **Scientific evidence** |
| Genotype 4 | SOF+PEG+RBV | 12 | Atomic neurino |
| SOF+LDV | 12 | Synergy |
| SOF+RBV | 12  24  (cirrhotics and nulls responders) | Egyptian |
| OBV+PTV+RBV (noncirrhotics) | 12 | Pearl-1 |
| Genotype 5 | SOF+PEG+RBV | 12 | Neutrino |
| Genotype 6 | SOF+PEG+RBV | 12 | Atomic |
| SOF+LDV | 16 | Electron-2 |