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**Future of liver disease in the era of direct acting antivirals for the treatment of hepatitis C**

Ponziani FR *et al.* Direct acting antivirals for the treatment of hepatitis C

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**Abstract**

Hepatitis C virus (HCV) infection has been a global health problem for decades, due to the high number of infected people and to the lack of effective and well-tolerated therapies. In the last three years, the approval of new direct acting antivirals characterized by high rates of virological clearance and excellent tolerability has dramatically improved HCV infection curability, especially for patients with advanced liver disease and for liver transplant recipients. Long-term data about the impact of the new direct acting antivirals on liver fibrosis and liver disease-related outcomes are not yet available, due to their recent introduction. However, previously published data deriving from the use of pegylated-interferon and ribavirin lead to hypothesize that we are going to observe in the future a reduction in mortality and in the incidence of hepatocellular carcinoma, as well as a regression of fibrosis for people previously affected by hepatitis C. In the liver transplant setting, clinical improvement has already been described after treatment with the new direct acting antivirals, which has often led to patients delisting. In the future, this may hopefully reduce the gap between liver organs request and availability, probably expanding liver transplant indication to other clinical conditions. Therefore, these new drugs are going to change the natural history of HCV-related liver disease and the epidemiology of HCV infection worldwide. However, the global consequences will depend on treatment accessibility and on the number of countries that could afford the use of the new direct acting antivirals.

**Key words:** Direct acting antivirals; Hepatitis C; Liver transplantation; Hepatocellular carcinoma; Liver fibrosis; Cirrhosis

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**Core tip**: The approval of new direct acting antivirals with high rates of virological clearance and excellent tolerability has dramatically improved HCV infection curability, especially for patients with advanced liver disease and for liver transplant recipients. The aim of this review is to draw the possible future scenery in HCV-related liver disease, focusing our attention on the impact of second generation direct acting antivirals on liver fibrosis, hepatocellular carcinoma and liver transplantation.

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**INTRODUCTION**

Since its discovery, hepatitis C virus (HCV) has been a constant burden for global health with 3 to 4 million of new infections each year and an overall number of 130-170 million of infected people in the world[[1](#_ENREF_1)]. The prevalence of HCV infection has a large geographical variability, ranging from less than 1% to more than 10% in different regions[[2](#_ENREF_2),[3](#_ENREF_3)]. In particular, 2.3 million of chronically infected subjects have been estimated in the United States, 1.5 in Japan and 11.5-19 in Europe[[4](#_ENREF_4)].

HCV infection becomes chronic in up to 50%-80% of cases, establishing a damage that may lead to cirrhosis and its complications (*e.g.,* hepatocellular carcinoma, portal hypertension, liver decompensation and insufficiency) in approximately 10%-20% of patients[[5](#_ENREF_5),6]. Nevertheless, chronic HCV infection may be associated with extrahepatic manifestations, such as cryoglobulinemia and non-Hodgkin lymphoma, mainly caused by the continuous stimulation of the immune system[[7](#_ENREF_6) - 8].

Non-pegylated interferon (IFN) or pegylated IFN (PEG-IFN) in combination with ribavirin (RBV) have been the main pharmacological agents for the treatment of hepatitis C infection. However, only 30%-40% of subjects with genotype 1 HCV and 70%-90% of those with genotype 2 and 3 treated with PEG-IFN in association with RBV were able to reach a sustained virological response (SVR), defined as the absence of detectable levels of HCV-RNA 24 wk after the end of treatment[[9-1](#_ENREF_12)4]. In 2011 the association of the first-generation direct acting antivirals (DAAs) Boceprevir and Telaprevir with PEG-IFN and RBV increased the overall SVR rates to 68%-75% for naive and to 59%-88% for treatment experienced patients, even if these regimens were dedicated just to the treatment of genotype 1 HCV infection[[1](#_ENREF_16)2,[1](#_ENREF_18)4,[1](#_ENREF_19)5]. However, the suboptimal response rates, the long duration of treatment (24 - 48 wk) and the scarce tolerability of Boceprevir and Telaprevir, especially by cirrhotic patients, heavily affected their clinical use and has led to search for new drugs[16].

**SECOND GENERATION DIRECT ACTING ANTIVIRALS**

The second-generation DAAs are characterized by elevated SVR rates, good safety profiles, and more comfortable types of administration. They can be used or not in combination with RBV, depending on virological and diasease-associated characteristics[[1](#_ENREF_21)7]. Sofosbuvir (SOF) has been the first new agent approved by FDA in December 2013 (Table 1 and Figure 1)[[18](#_ENREF_22)].

SOF targets HCV-RNA replication with a pangenotypic efficacy since it blocks the nucleotide polymerase inhibitor NS5B, which is highly preserved among different HCV genotypes[19]. Treatment with SOF, either in combination with PEG-IFN plus RBV or with RBV alone has shown SVR rates above 85% 12 weeks after the end of treatment (SVR12)[[2](#_ENREF_25)0]. Successively, new DAAs for the treatment of HCV infection in association with SOF have been approved: Simeprevir (SMV, a NS3/4A protease inhibitor) and Ledipasvir (LDV, a NS5A inhibitor) for genotype 1, and Daclatasvir (DCV, a pangenotypic NS5A inhibitor) for genotype 3, reporting SVR12 rates above 90%[[21-2](#_ENREF_26)4]. More recently, Velpatasvir (VEL) has also been approved for HCV treatment in combination with SOF[[2](#_ENREF_29)5,[26](#_ENREF_30)].

The first antiviral regimen SOF-free was approved in July 2015 and includes Paritaprevir (a NS3/4A protease inhibitor), Ritonavir (a CYP3A inhibitor, used as a pharmacologic booster) and Ombitasvir (a NS5A inhibitor), in association with Dasabuvir (a non-nucleoside NS5B polymerase inhibitor), and is indicated for the treatment of genotype 1 (with Dasabuvir) and 4 (without Dasabuvir) HCV infection[[27](#_ENREF_31),[28](#_ENREF_32)]. Successively, FDA has approved another SOF-free antiviral regimen including Elbasvir and Grazoprevir[29], and new drugs with pangenotypic efficacy are in final phase of study and will soon be available [[30](#_ENREF_30)].

The main advantage of the new DAAs-based antiviral regimens is the achievement of high SVR rates for all HCV genotypes within a short treatment period, together with the infrequent occurrence of side effects, usually of mild grade. Resistance-associated variants (RAVs) of the virus may exist prior to treatment, may persist for years after treatment and affect most frequently the NS3/5A viral protein; RAVs are associated with (but do not inevitably result in) treatment failure, which may occur in about 10%-15% of patients[3[1](#_ENREF_30),32].

The most ambitious result we might expect from the use of DAAs would be the reduction of liver cirrhosis-related complications, such as hepatocellular carcinoma (HCC) development, and in the long-term period a decreased progression towards end-stage liver disease and a decreased need for liver transplant (LT), as well as the prevention of post-LT HCV infection recurrence[3[3](#_ENREF_12)]. Indeed, according to the latest data published by the WHO in 2013, 5%-7% of infected subjects die from a disease related to HCV[[3](#_ENREF_38)4], with an estimated risk of liver failure of 10.4% and 26.5% in patients with F3 and F4 fibrosis, respectively[[3](#_ENREF_39)5]. HCV-associated liver disease represents the most common indication for LT and, in developed countries, is the most common etiological factor of hepatocellular carcinoma, which is the third leading cause of cancer death worldwide[36-40].

However, due to the relatively recent introduction of these new drugs, data about their impact on liver disease progression, complications and liver-related mortality are scarce. Therefore, previously published data about the impact of SVR achieved with PEGIFN-based regimens are the only available reference to evaluate the future positive effects that DAAs might produce on liver disease outcomes.

# IMPACT OF VIRAL ERADICATION ON LIVER CIRRHOSIS ASSOCIATED MORBIDITY AND MORTALITY

Published data have demonstrated a correlation between the achievement of SVR and the reduction of HCV-related complications, liver disease severity and mortality (Table 2).

Veldt *et al*[41] reported that among 286 subjects who achieved a SVR followed-up for 5 years only 1% experienced liver failure, with a survival similar to that of the general population. Another study including 721 patients with chronic hepatitis C reported a significantly lower annual mortality rate in subjects who had previously achieved a SVR after IFN therapy compared to those who had not (0.44%/year, 1.98%/year and 3.19%/year for SVR, non-SVR and untreated patients, respectively; *P* < 0.0001). The study also showed that viral clearance was able to reduce the hazard ratio for total deaths by 0.173[42].

A meta-analysis including 129 trials for a total amount of 15067 patients has demonstrated that SVR achievement reduces the risk of liver transplant requirement by 90%, and produces a total reduction of the risk of death by 60%-84%[[41](#_ENREF_51)]. Nevertheless, viral clearance leads to a lower incidence of liver-related morbidity and death (0.62, and 0.61 among SVR patients, respectively, and 4.16, and 3.76 among non-SVR patients, respectively, *P*< 0.001) [4[4](#_ENREF_52)]. Recent data further confirmed that HCV infection resolution allows to reduce the incidence of liver decompensation[4[5](#_ENREF_52)], all-cause mortality[46,47] and annual deaths rate (8.9% in SVR patients *vs* 26.0% in non-SVR ones, *P* <0.001)[[4](#_ENREF_53)8]. This evidence was confirmed by an extensive review by Szabo and colleagues[[3](#_ENREF_38" \o "Szabo, 2015 #263)4]; moreover, survival rates comparable to general population have been reported after the achievement of SVR even in patients with well-compensated cirrhosis[49]. Although useful to figure out the long-term benefits expected from DAAs, the interpretation of data emerging from IFN- or PEG-IFN-based regimens is limited by the selection of patients, since those affected by comorbidities were usually not suitable for treatment and were not included in outcomes analyses; moreover, the lack of homogeneous design and patients’ stratification make difficult to deduce general conclusions.

**IMPACT OF VIRAL ERADICATION ON LIVER FIBROSIS**

Despite the positive impact of HCV infection eradication on patients’ prognosis, few data about liver cirrhosis/fibrosis regression are available.

The regression of liver fibrosis as a result of viral clearance is supported by the reduction of inflammatory mediators that leads to the apoptosis of myofibroblasts, and by the inactivation of stellate cells. The downregulation of inflammation, as well as~~-~~microvascular remodelling, degradation of extra-cellular matrix and hepatocytes repopulation lead to the generation of new hepatic tissue[50,51].

Cirrhosis regression has been reported in about 61% of cases after a median time of 3 years from the achievement of SVR (Table 2)[52]. Mallet *et al*[[5](#_ENREF_57)3] observed the evolutionof liver fibrosis in 96 patients treated with IFN or PEG-IFN with or without RBV, for a median follow-up of 118 months. Although statistical significance was not reached, 18 subjects obtained a regression of fibrosis from METAVIR stage 4 to stage ≤ 2. In another study, among 153 cirrhotic patients treated with IFN or PEG-IFN in combination or not with RBV for 24 or 48 weeks, 75 (49%) had a regression of fibrosis after a mean time of 21±4 months. In addition to SVR, factors independently associated with histology improvement were age < 40 years (*P* < 0.001) and a body mass index < 27 kg/m2 (*P* < 0.001) [[5](#_ENREF_58)4].

Other small studies reported variable rates of fibrosis regression after different time periods from viral clearance[55-62].

However, the neo-formed parenchyma derived from the generation of new liver tissue is different from the healthy one and is characterized by architectural and structural alterations[63]. At present, little is known about its functionality.

**IMPACT OF VIRAL ERADICATION ON THE DEVELOPMENT OF HEPATOCELLULAR CARCINOMA**

In HCV infected subjects the development of liver cirrhosis is the main oncogenic trigger for HCC[[5](#_ENREF_5),[6](#_ENREF_49)4,[6](#_ENREF_67)5], though not the only one. Indeed, direct and indirect viral-related mechanisms may contribute to the growth of cancer cells: the expression of viral proteins with oncogenic effect from infected-cells, messy proliferation of non-infected hepatocytes responsive to the apoptotic boost and the oxidative stress caused by inflammation[[6](#_ENREF_68)6].

The first study documenting the importance of viral clearance in reducing the risk of HCC development was published in 1995. Ninety HCV infected subjects, half of whom have undergone antiviral therapy with IFN, were followed-up for 5 years; 17 untreated subjects developed HCC compared with only 2 of those treated[[6](#_ENREF_69)7]. A subsequent study also reported a significant difference in HCC occurrence between SVR and non-SVR patients (5.1% and 21.8%, respectively, *P* < 0.001)[4[8](#_ENREF_53)]. A recent meta-analysis including 31528 patients with a median follow-up ranging from 3 to 8 years demonstrated that SVR is a key factor in reducing the risk of HCC development, since among responders only 1.5% developed tumor lesions compared to 6.2% of non-SVR patients[68]. Moreover, considering only those subjects with advanced fibrosis (F3-F4 according to Metavir score), the incidence of HCC was of 17.9% among non-responders, four times greater than the 4.2% rate reported among responders (*P* < 0.001).

HCV eradication may also reduce the risk of HCC recurrence after surgical treatment. A 63.4% cumulative recurrence rate has been reported in non-treated patients compared to 63.2% in treated ones who did not achieve a SVR, and to 41.7% in the SVR group (non-treated *vs* SVR, *P* = 0.008; SVR *vs* treated without SVR, *P* = 0.035)[69]. Mazzaferro *et al*[70] also found SVR as the only factor significantly reducing HCC late recurrence in HCV-pure (hepatitis B anticore antibody negative)patients. A subsequent meta-analysis also reported a reduced rate of early recurrence in 51 patients undergoing surgical resection or percutaneous ablation, reporting a 30% reduction in HCC recurrence rate[71]. In addition, IFN therapy seems to exert beneficial effects even when started before HCC curative treatments[72].

Although based on heterogeneous studies, these data have raised the issue of the favourable properties of IFN in the prevention of HCC development and recurrence. IFN seems to combine antiviral and antiproliferative effects, such as inhibition of angiogenesis, enhancing of antitumoral immunity and induction of pro-apoptotic boost[70,[7](#_ENREF_75)3]. Recent data have highlighted that IFN may prevent postoperative recurrence of HCC expressing Metastatic Tumor antigen 1 (MTA1), being 1-year recurrence rate as high as 7% in IFN-treated compared to 24% in the control group (*P* < 0.05)[[7](#_ENREF_76)4].

DAAs may probably modulate the expression of genes involved in the production of endogenous IFN. Patients treated with SOF in association with RBV a reduction in types I and II IFN in liver tissue and an increase of IFN-alpha2 have been observed[[7](#_ENREF_77)5]. Conversely, other Authors reported a loss of intrahepatic immune activation by IFN-gamma, associated with normalization of NK‑cell phenotype and function, consequent to DAAs treatment[[7](#_ENREF_77)6]. How these findings may be associated with DAAs treatment outcome still needs to be further elucidated.

Although the risk of HCC development is significantly reduced by viral clearance it is not completely eliminated, especially in case of persistence of other cofactors promoting carcinogenesis. Toyoda *et al*[[7](#_ENREF_78)7] reported that 18/522 patients who achieved a SVR after IFN treatment developed HCC after a median follow-up of about 7.2 years (1.0 - 22.9 years), with an incidence of 1.2% and 4.3% at 5 and 10 years respectively. In the analysis, the presence of diabetes mellitus and advanced fibrosis (FIB-4 index ≥ 2) at 24 wk after SVR were correlated to an increased risk of developing HCC. Other data identified type 2 diabetes mellitus and total alcohol intake as independent risk factors for HCC development (HR 2.77, 95%CI: (2.13 – 3.60), *P* < 0.001 and HR 2.13 95%CI: (1.74 – 2.61), *P* < 0.001, respectively)[78]. In another study[79], among 232 SVR patients who underwent liver biopsy between 1992 and 2009, the development of HCC was definitively lower in the group with low-intermediate grade fibrosis (F0-F2 according to Metavir) than in that with F3-F4 grade (1.6% and 8%, respectively).

In contrast with the favourable effect of viral clearance on HCC development, it has been recently reported an increased incidence of HCC recurrence in patients with previously treated nodules receiving DAAs therapy[80-82], while other studies have not supported this evidence[[8](#_ENREF_82)3,84]. However, these data need to be further confirmed, and an investigation focused on the immunologic changes and the microenvironmental hepatic tissue alterations consequent to DAAs treatment is probably worthwhile[[8](#_ENREF_82)5].

**DIRECT ACTING ANTIVIRALS AND LIVER TRANSPLANTATION**

HCV infection-associated cirrhosis and HCC account for 40% of all cases on the waiting list in the United States and for about 1/3 of LT in cirrhotic patients[39,40]. HCV infection recurrence of the graft is universal and leads to cirrhosis in up to 20%-30% of recipients, being one of the most important causes of death and retransplantation[[8](#_ENREF_84)6,87]. The time course of post-LT HCV reinfection is faster than among immunocompetent individuals: cirrhosis can be histologically documented within 5 years after LT and from that point on, the first episode of decompensation may occur within less than one year[[8](#_ENREF_85)8].

After HCV infection eradication, a 62%-84% decrease in 5-year mortality as well as a reduction by 90% of the risk of receiving LT have been reported [[4](#_ENREF_51)3]. This improvement in survival was observed in both sustained virological responders and relapsers[[8](#_ENREF_86)9]. The new available DAAs account for response rates higher than 90% and are better tolerated compared to IFN and PEG-IFN, allowing to treat patients for whom the previous antivirals were contraindicated and who had low chances of response due to unfavorable virological or clinical conditions[90]. As patients who achieve SVR have a reduced risk of progression to cirrhosis and of developing its complications, the widespread use of the new DAAs will probably change the scenario of LT, potentially reducing the need for liver organs.

***DAAs treatment before liver transplantation***

The aim of antiviral treatment in patients on the waiting list is to prevent the recurrence of HCV infection after LT. To reduce the risk of post-LT recurrence, the achievement of at least 30 d of HCV-RNA negativity before LT has been suggested[91,92]. However, whether it is necessary to continue antiviral therapy after LT in patients who received a very short course of therapy before transplantation is not yet clear[93].

Furthermore, achieving a SVR in waiting-list patients may directly impact on the severity of liver disease, with possible delisting after treatment. A recent real-life multicenter study[94] including 103 decompensated cirrhotic patients listed for LT and treated with second generation DAAs, reported HCV eradication rates of 16% at 24 wk and of 35% at 48 wk after the beginning of treatment (Table 3). This was associated with delisting of 20% of patients at 48 wk from the end of treatment. The evidence of a significant improvement of liver function also comes from the SOLAR-1 study cohort A[95], including cirrhotic patients with decompensated disease treated with LDV and SOF plus RBV. In this study, similar SVR rates (from 86% to 89%) have been reported by Child-Pugh class B and C patients regardless of treatment duration, and this was associated with the improvement of MELD and Child-Pugh scores.

Other studies confirmed liver function amelioration after viral eradication in decompensated cirrhotic patients[26,95-[101](#_ENREF_91)], although in cases with more advanced liver impairment (Child-Pugh C, albumin lower than 3.5 g/dL, MELD > 20) and in the elderly worsening of liver function has also been reported[102,103].

Delisting due to clinical improvement may therefore become frequent in the era of DAAs, making possible to reserve LT only to patients who do not show significant benefit. Munoz *et al*[104] estimated that DAAs-induced reduction in MELD score down to the threshold of LT benefit may occur in 592-993 listed patients/year during the first year after treatment, and that approximately 213-515 donated livers/year may become available for redistribution to other patients.

The future impact of DAAs on indications for LT and on organs allocation policy may depend not only on the decreased number of HCV infected recipients but also on the potential use of anti-HCV positive donors[105]. Indeed, DAAs might introduce a new era, in which anti-HCV positive donors could be reconsidered as a potential source of liver grafts. Moreover, in case of HCV infection transmission from anti-HCV positive donors during LT, it may be easily cured[105]. Recent data suggest that LT outcomes for recipients who accept HCV-positive allografts could be comparable with those of recipients who received HCV-negative allografts[106,[10](#_ENREF_101)7]. Probably, in the future, histological evaluation may become crucial in the choice and the allocation of liver grafts from anti-HCV positive donors, overcoming the issue of previous or active HCV infection. However, these considerations are based on the universal adoption of screening policies for HCV infection, as well as on the widespread use of DAAs for HCV infection treatment, which isstill limited by restricted accessibility.

***DAAs treatment after liver transplantation***

DAAs have demonstrated unprecedented results in the treatment of LT recipients (Table 4).

The SOLAR-1 study, cohort B[95], explored the efficacy of LDV and SOF plus RBV in the treatment of LT recipients without cirrhosis (group 3), with compensated cirrhosis (group 4), and with Child-Pugh B (group 5) and C cirrhosis (group 6). In groups 3 and 4 SVR rates ranged from 96% to 98% independently of treatment duration; in group 5, SVR was achieved by 86% of patients who received 12 weeks of treatment and by 88% of those who received 24 wk of treatment; group 6, instead, had lower rates of SVR, being 60% and 75% in patients receiving 12 and 24 wk of treatment, respectively.

Another study with a similar design, the SOLAR-2, also reported excellent SVR rates in LT recipients with decompensated cirrhosis and genotype 1 or 4 HCV infection treated with LDV and SOF plus RBV for 12 or 24 wk[[9](#_ENREF_91)8].

The ALLY-1 and the HCV-TARGET study confirmed good outcomes also for the combination regimens including SMV plus SOF with or without RBV and DCV plus SOF with RBV[[9](#_ENREF_92)7,108].

Although these data may highlight that the achievement of SVR is more difficult in LT cirrhotic patients with more advanced liver impairment, the SOLAR-1 and 2 studies also reported an improvement in MELD and Child-Pugh scores in treated patients[95,98]. This was confirmed by a prospective, multicenter study in patients with post-LT hepatitis C recurrence treated with LDV and SOF plus RBV: the response rate was 96% in Child Pugh A patients compared to 85% and 65% in Child Pugh Class B and C ones, respectively. However, an improvement in Child-Pugh class and MELD scores was observed in patients with decompensated cirrhosis who achieved SVR12[[10](#_ENREF_104)9].

Therefore, liver function improvement consequent to antiviral treatment will hopefully reduce the need for retransplantation and the morbidity and mortality related to liver dysfunction and liver cirrhosis complications.

**HCV INFECTION AND DISEASE-RELATED COMPLICATIONS IN THE FUTURE**

The future trend of the HCV-related morbidity and mortality in the era of IFN-free antiviral regimens is difficult to predict, although encouraging prospects can be inferred by recent data and projections.

Sievert *et al*[[110](#_ENREF_104)] recently analysed the future effects of the increase in SVR rates in the Australian population, taking into account three different models: without increasing (first scenario) or increasing (second scenario) the number of treated patients and, finally, considering treatment prescription restricted to patients with fibrosis ≥ F3 only (third scenario).

Applying the model of restricted prescription in the time period between 2015 and 2017, an estimated reduction by 51% of HCC development and by 56% and 54% of compensated and decompensated cirrhosis could be expected in 2030, respectively, as well as a 56% decrease in mortality rates. The cumulative costs of HCV infection were reduced by 26% from the base case. If the time span was extended to all years, a 90% decrease in compensated and decompensated liver cirrhotic patients was expected by 2030, with a reduction of HCC by 84%. In absence of eligibility restriction, chronically infected people were estimated to reduce by 60% in 2030, with a slightly lower decrease of cases of cirrhosis and HCC and comparable cumulative costs reduction.

A similar study conducted on the French population analysed the reduction in the need for LT associated with HCV infection treatment. Based on two main scenarios constructed by estimating the number of LT candidates between 2013-2022, the Authors demonstrated that antiviral treatments will avoid 4425 transplants reducing by 45% and by 88% the gap between liver organs request and availability for patients with decompensated cirrhosis and HCC, respectively. This will allow to satisfy the LT demand for patients affected by HCC within 2022, although the same results cannot be probably achieved for decompensated cirrhotic patients[[111](#_ENREF_106)].

Finally, Kabiri *et al*[[1](#_ENREF_106)12] published a transition model analysis to predict the effect of HCV therapies in the United States. Compared to a scenario including new therapies but with limited treatment capacities and risk-based or birth-cohort screening, a scenario with universal screening and absence of treatment limitations was able to prevent 91000 cases of HCC, 128800 cases of decompensated cirrhosis, 153200 liver-related deaths, and 13400 LT. The Authors concluded that HCV might be destined to become a rare disease within 2036.

Although the major limitation of these studies is represented by the correct estimation of treatment response rates, as well as by the quantification of treatment costs, which are in constant evolution, they may provide a useful projection of the evolution of HCV-related health and economic burden in the near future.

**CONCLUSION**

The discovery of DAAs has radically changed the world scene of hepatitis C infection and its associated morbidity and mortality.

The current evolution and revolution of HCV antiviral treatment has increased the number of patients achieving viral eradication and, therefore, is going to reduce the incidence of cirrhosis, the rate of liver decompensation and HCC development, as well as patients’ mortality. This will probably lead to a decrease of the need for LT, providing an adequate supply for nearby all patients with HCC and part of those with decompensated cirrhosis. The future widespread use of these new antivirals might also influence the policy of donor selection, leading to the expansion of the pool of available liver organs, since HCV infection may represent no more a contraindication for the use of liver grafts.

Although DAAs have made possible to envisage a bright future in the fight against HCV-related liver disease, only long-term follow-up studies will allow to accurately quantify the benefit produced. The assessment of the less evident changes produced by the new antivirals, such as microenvironmental and immunologic changes produced in the liver, is also mandatory, to predict and avoid the occurrence of possible unexpected consequences.

Finally, the disparity in the use of DAAs throughout the world caused by the high costs and the restricted availability makes difficult to draw definitive conclusions about the future epidemiology and evolution of HCV-related liver disease worldwide.

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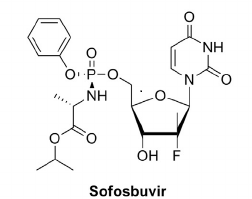
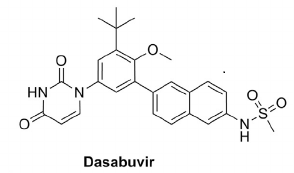
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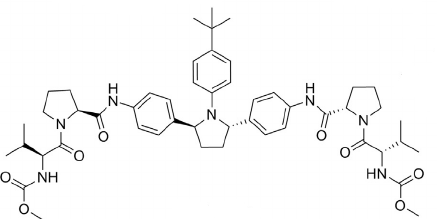
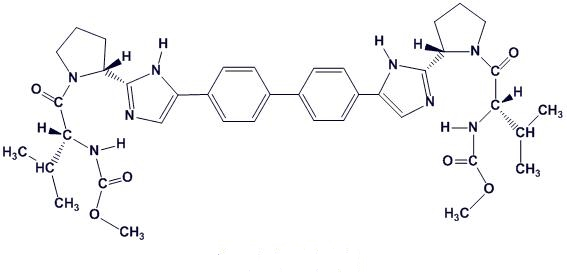
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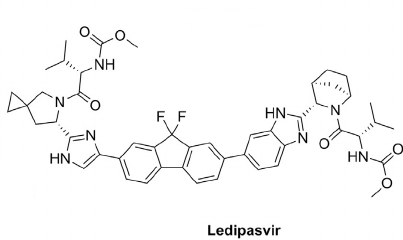
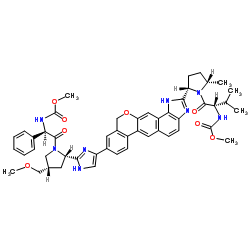
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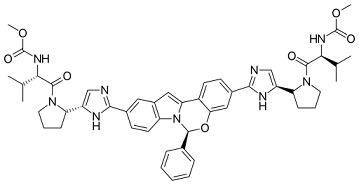
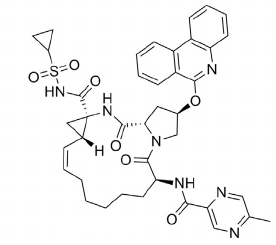
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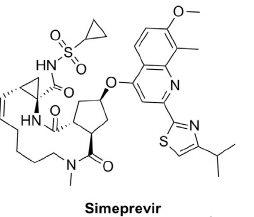
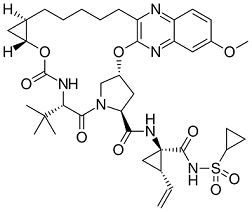
Ombitasvir Daclatasvir

Ledipasvir Velpatasvir

Elbasvir Paritaprevir

Simprevir Grazoprevir

**Figure 1 Second generation direct acting antivirals molecule.**

**Table 1 Main features ant viral targets of second generation direct acting antivirals**

| MOLECULE Molecule | Class | Target | Genotype | Associations |
| --- | --- | --- | --- | --- |
| Sofosbuvir | Nucleotide polymerase inhibitor (NPIs) | NS5B RNA-dependent RNA polymerase | pangenotypic | Ledipasvir  Daclatsvir  Simprevir  Velpatasvir |
| Dasabuvir | Non-nucleoside polymerase inhibitor (NNPIs) | NS5B RNA-dependent RNA polymerase | genotype 1 | Ombitasvir+ Paritaprevir+ Ritonavir |
| Ombitasvir |  | NS5A | genotype 1,4 | Paritaprevir+ Ritonavir with or without Dasabuvir |
| Daclatasvir |  | NS5A | genotype 2,3 | Sofosbuvir |
| Ledipasvir |  | NS5A | genotype 1,3,4 | Sofosbuvir |
| Velpatasvir |  | NS5A | pangenotypic | Sofosbuvir |
| Elbasvir |  | NS5A | pangenotypic | Grazoprevir |
| Paritaprevir |  | NS3/4A protease | genotype 1,4 | Ombitasvir+ Ritonavir with or without Dasabuvir |
| Simprevir |  | NS3/4A protease | genotype 1,4 | Sofosbuvir |
| Grazoprevir |  | NS3/4A protease | pangenotypic | Elbasvir |

**Table 2 Main studies highlighting the effects of HCV antiviral therapy on patients’ mortality, fibrosis regression and risk of hepatocellular carcinoma**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **HCV genotype** | **Fibrosis stage** | **Treatment** | **SVR rate** | **Mortality (n pts)** | **Survival** | **Other Outcomes** |
| Veldt *et al*[[47](#_ENREF_47)], 2007 | G1: 280/474 (59%) | Ishak score 4: 120 (25%)  Ishak score 5: 94 (20%)  Ishak score 6: 265 (55%) | Duration of treatment, 26 week (21-48)  IFN: 131 (27%)  IFN + RBV: 130 (27%)  PEG-IFN: 10 (2.1%)  PEG-IFN + RBV: 208 (43%) | 142/280 (50.7%) | SVR: 2/280 (0.7%)  Non-SVR: 24/280 (8.6%) | - | SVR associated with reduction in the hazard of events (adjusted HR 0.21, 95%CI: 0.07-0.58;  *P* < 0.003) |
| Yoshida *et al*[[64](#_ENREF_47)] 1999 | G1: 1177/2400 (49%)  G2: 496/2400 (20.6%) | F0: 45 (1.9%)  F1: 665 (27.7%)  F2: 896 (37.7%)  F3: 564 (23.5%)  F4: 230 (9.6%) | IFN-α: 84%  IFN-β: 14%  combination of IFN-α and IFN-β: 2% | 789/2400 (32.8%) | - | - | Risk of HCC for IFN therapy: adjusted risk ratio, 0.516, 95%CI: 0.358-0.742 (*P* < 0.001); risk of HCC for SVR pts: risk ratio 0.197, 95%CI: 0.099-0.392 (*P* < 0.002) |
| Veldt  *et al*[[41](#_ENREF_47)] 2004 | SVR  G1: 112/286 (39.2%)  not specified: 174/286 (60.8%)  Non-SVR  G1: 21/50 (42%)  not specified: 29/50 (58%) | SVR:  F4: 15 (5.2%)  Non-SVR:  F4: 11 (22%) | Recombinant IFN α2a, α2b, or natural IFN monotherapy for 39 weeks | 286 | SVR  6/286 (2.1%)  non-SVR  3/50 (6%) | SVR group: comparable with the general population | 29% regression and  5% progression of fibrosis in SVR group |
| Maruoka  *et al*[[42](#_ENREF_47)] 2012 | Treated (577):  G1: 383/577 (66.2%)  G2: 144/577 (24.8%)  Untreated (144) | Treated:  F0: 15 (2.6%)  F1: 290 (503%)  F2: 132 (22.9%)  F3: 82 (12.2%)  F4 58 (10.1%)  Untreated:  F0:2 (1.4%)  F1: 64 (44.4%)  F2:32 (22.2%)  F3:18 (12.5%) | IFN (not specified) | 221/577 (38.3%) | Untreated: 37/144 (25.7%)  non-SVR  74/356 (20.8%)  SVR 10/221 (4.5%) | - | Risk ratio of overall death and liver-related death reduced to 0.173 (95%CI: 0.075–0.402) |
| Bruno *et al*[[49](#_ENREF_47)], 2016 | G1: 88/181 (48.6%) | F4: 100%  CPT A5: 154/181 (85.1%)  CPT A6: 27/181 (14.9%) | IFN mono-therapy or IFN (pegylated or not) + RBV | 181 | 18/181 (9.9%) | - | - |
| Cardoso  *et al*[[44](#_ENREF_47)], 2010 | G1: 60%  G2: 8%  G3: 16%  G4: 13% | F4: 54% | PEG-IFN +RBV: 252 (82%), PEG-IFN: 22 (7%),  IFN +/- RBV: 33 (11%) | 103/307 (33.5%) | 21/307 (6.8%) | - | - |
| Tada  *et al*[[46](#_ENREF_47)], 2016 | G1: 1476/2743 (53.8%)  G2: 789/2743 (28.3%)  unknown: 478/2743 (17.4%) | - | IFN (not specified) | 587/2267 (25.9%) | 137/2267 (6%) | - | - |
| Van der Meer  *et al*48], 2012 | G1: 340/498 (68.3%)  G2: 48/498 (9.6%)  G3: 88/498 (17.7%)  G4: 22/498 (4.4%) | Ishak 4: 143/498 (27%)  Ishak 5: 101/498 (19%)  Ishak 6: 22/498 (4%) | IFN: 175 (33%)  IFN + RBV: 148 (28%)  PEG-INF: 176 (33%)  PEG-IFN + RBV: 176 (33%) | 192/498 (38.5%) | SVR: 13  non-SVR: 100 | - | SVR reduced all-cause mortality (HR = 0.265, 95%CI: 0.14-0.49;  *P* < 0.001) |
| D’Ambrosio  *et al*[[52](#_ENREF_47)], 2012 | G1: 11/38 (28.9%)  G2: 24/38 (63.2%)  G3: 3/38 (7.9%) | Only cirrhotic patients | IFN+RBV: 10/38 (26.3%)  PEG-IFN+RBV:  28/38 (73.6%)  Duration of treatment 24 months (24-48) | - | - | - | SVR reduced area of fibrosis by 2.3% (*P* < 0.0001), with a median individual decrease of 71.8%. |
| Mallet  *et al*[[53](#_ENREF_47)], 2008 | G1: 51/96 (53.1%) | F4: 100% | IFN or PEG-IFN, with or without RBV | 39/96 (40.6%) | SVR: 4 (10.2%)  non-SVR:17 (29.8%) | - | Regression of fibrosis (according to METAVIR score): stage 4: 69 (71.9%);  stage 3: 9 (9.4%);  stage 2: 10 (10.4%); stage 1: 7 (7.3%); stage 0: 1 (1%). |
| Reichard O *et al*[[56](#_ENREF_47)], 1999 | G1: 41/100 (41%)  G2: 27/100 (27%)  G3: 23/100 (23%)  mixed: 9/100 (9%) | F 0-3: 22  F4: 4 | IFN alpha2b: 73  Human leucocyte IFN alpha: 42 | 27/100 (27%) | - | - | Reduction of portal inflammation (*P* < 0.0002), piecemeal necrosis (*P* < 0.0004), lobular necrosis (*P* < 0.0005), fibrosis (*P* < 0.0008) after SVR |
| Arif  *et al*[[57](#_ENREF_47)], 2003 | Naive (52):  G1a:64%  G1b:19%  G2: 6%  G3: 10%  G4: 1%  Experienced (79):  G1a:55%  G1b:26%  G2:7%  G3: 10%  G4:2% | Naive  fibrosis score: 2.91 ± 1.64 | IFN alpha2b  Duration of treatment:  12–24 weeks: 10  24 weeks: 56  36 weeks: 8  48 weeks: 30 | Naive  21/52 (40.4%)  Experienced  18/79 (22.8%) | - | - | Reduction in fibrosis score in both groups: responders = −0.91 (*P* = 0.038), non-responders = −0.48 (*P* = 0.021) |
| Fibrosis score: 2.83 ± 1.62 |
| George *et al*[[58](#_ENREF_47)], 2009 | G1: 75/141 (53%)  G2: 49/141 (35%)  G3: 14/141 (10%)  G4: 3/141 (2%) | Fibrosis stage ≥ 2: 116  Fibrosis stage = 4: 16  according to Scheuer | IFN alpha2b+RBV: 146 (97%)  PEG-IFN alpha2a + RBV:  4 (3%) | 100% | - | 1 | 39/49 (79.6%) Reduction in fibrosis stage (according to Ishak score).  16/49 (32.6%) pts had 2 point or greater decrease in stage |
| Poynard *et al*[[59](#_ENREF_47)], 2002 | - | Standard:  F0: 12 (15%)  F1: 42 (54%)  F3: 24 (31%)  F4: 0 (0%)  Reinforced:  F0: 16 (18%)  F1: 41 (47%)  F3: 30 (35%)  F4: 0 | Standard:  IFN alpha2a 3 MU  TIW for 24 wk  Reinforced:  IFN alpha2a 6 MU daily for 12 days followed by thrice weekly for 22 weeks, then 3 MU thrice weekly for 24 weeks. | Standard:  3/78 (3.8%)  Reinforced:  14/87 (16%) | - | - | Decrease in fibrosis index score in SVR group compared with non-responders: from 0.33 ± 0.06 at baseline to 0.18 ± 0.06 at 72 wk *vs* from 0.41 ± 0.03 at baseline to 0.44 ± 0.03 at 72 wk (p < 0.001) |
| Shiratori  *et al*[[60](#_ENREF_47)], 2000 | - | SVR:  F0: 3 (2%)  F1: 42 (23%)  F2: 69 (37%)  F3: 45 (25%)  F4: 24 (13%)  Non-SVR:  F0: 3 (1%)  F1: 95 (31%)  F2: 109 (36%)  F3: 67 (22%)  F4: 30 (10%) | IFN alpha2a or  IFN alpha2b or  natural IFN alpha weekly for 3 to 6 mo  IFN alpha six to seven times per week for 8 wk | 183/487 (37.6%) | - | - | SVR group: rate of fibrosis progression -0.28 ± 0.03 unit/year (regression)  Non-SVR group: rate of fibrosis progression: 0.02 ± 0.02 unit/year  *P* < 0.001 |
| Maylin  *et al*[[62](#_ENREF_47)],  2008 | G1: 21/210 (39%)  G2: 55/210 (18%)  G3: 101/210 (32%)  G4-5: 33/210 (11%) | F0-1: 121 (38%)  F2: 111 (35%)  F3: 56 (17%)  F4: 31 (10%) | IFN alpha: 3 (1%)  IFN-lymphoblastoid: 5 (1%)  IFN-hybrid: 9 (3%)  IFN alpha2a: 18 (5%)  IFN alpha2a + RBV: 5 (2%)  PEG–IFN alpha2a + RBV: 27 (8%)  IFN alpha2b: 22 (6%)  IFN alpha2b + RBV: 41 (12%)  PEG–IFN alpha2b + RBV: 214 (62%) | 100% | - | - | Fibrosis stage improved in 56%, stable in 32%, deteriorated in 12%.  Regression of cirrhosis observed in 9 of 14 (64%). |

Pts: patients; IFN: Interferon; PEG-IFN: Pegylated Interferon; RBV: Ribavirin; SVR: Sustained Virological Response; HCC: Hepatocellular Carcinoma.

**Table 3** **Main studies evaluating the effects of direct acting antivirals in patients with advanced cirrhosis and/or listed for liver transplantation**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **HCV genotype** | **Fibrosis stage** | **Treatment** | **SVR rate** | **Observed improvement** |
| Charlton *et al*[9[5](#_ENREF_91)], 2015 | Cohort A  G1a: 74/108 (68.5%)  G1b: 31/108 (28.7%)  G4: 3/108 (2.8%) | Child A: 1/108 (1%)  Child B: 65/108 (60.2%)  Child C: 42/108 (38.9%) | LDV/SOF + RBV 12 or 24 wk | Child B:  -12 wk 26/30 (87%)  -24 wk 24/27 (89%)  Child C:  - 12 wk 19/22 (86%)  -24 wk 20/23 (87%) | - |
| Belli *et al*[94],  2016 | G1a: 20/103 (19.4%)  G1b: 40/103 (38.8%)  G2: 3/103 (3%)  G3: 20/103 (19.4%)  G4: 20/103 (19.4%) | Child A:0  Child B: 46/103 (44.7%)  Child C: 57/103 (55.3%) | SOF/RBV: 52/103 (50.4%)  SOF/LDV+-RBV: 9/103 (8.7%)  SOF/ DCV +-RBV: 35/103 (33.9%)  SOF/SMV+- RBV: 7/103 (6.8%) | SOF/RBV (24-48 wk): RVR 61%  EVR 98%  SOF+2nd DAA (12-24 wk):  RVR 67%  EVR 98% | MELD: - 3.4 points  Child: -2 points  Delisting: 20%  Improvement in refractory ascites that became treatable with diuretics |
| Munoz *et al*[104],  2015 | - | Only cirrhosis | SOF/LDV + RBV (12-24 wk): 230  DCV/SOF + RBV (12 wk): 56  GRZ/ELB (12 wk): 27  SOF/LDV/DCV +- RBV (12 wk): 220 | SVR 84% | MELD: -2.9 +- 0.1  Child B to Child A 35%  Child C to Child B 48% |
| Manns *et al*[98], 2016 | G1a: 50/107 (46.7%)  G1b: 47/107 (43.9%)  G4: 10/107 (9.4%) | Child A: 2/107 (2%)  Child B: 60/107 (56%)  Child C: 45/107 (42%) | LED/SOF + RBV 12 or 24 wk | Genotype 1  Child B: 12 wk 20/23 (87%); 24 wk 22/23 (96%)  Child C: 12 wk 17/20 (85%); 24 wk 18/23 (78%), 1/2 (50%) | MELD improvement in 72%  Child B to Child A 28%  Child C to Child B 68% |
| Genotype 4  Child B: 12 wk 2/3 (67%); 24 wk 100%  Child C 12 wk 0%  24 wk |
| Poordad *et al*[97],  2016 | G1a: 34/60 (56.7%)  G1b: 11/60 (18.3%)  G2: 5/60 (8.3%)  G3: 6/60 (10%)  G4: 4/60 (6.7%) | Child A: 12/60 (20%)  Child B: 32/60 (53.3%)  Child C: 16/60 (27.7%) | DCV/SOF + RBV 12 or 24 wk | Child A: 11/12 (92%)  Child B: 30/32 (94%)  Child C: 9/16 (56%) | MELD improvement in 47% of pts  Child improvement in 60% of pts |
| Jacobson *et al*[96], 2015 | PART 1  G1a: 27/30 (90%)  G1b: 3/30 (10%) | Only Child B cirrhosis | GRZ/ELB 12 wk | SVR 27/30 (90%) | MELD improvement in 11/30 (36.7%) pts |
| Curry *et al*[26], 2015 | G1a: 159/267 (59.6%)  G1b: 48/267 (18%)  G2: 12/267 (4.5%)  G3: 39/267 (14.6%)  G4: 8/267 (3%)  G6: 1/267 (0.3%) | Child A: 16/267 (6%)  Child B: 240/267 (89.9%)  Child C: 11/267 (4.1%) | SOF/VEL 12 or 24 wk  SOF/VEL+ RBV 12 wk | SOF/VEL 12 wk: 75/90 (83%)  SOF/VEL + RBV 12 wk: 82/87 (94%)  SOF/VEL 24 wk: 77/90 (86%) | MELD improvement in 51% of pts  Child improvement in 47% of pts |
| Gray *et al*[103], 2016 | G1a: 29/101 (28.7%)  G1b: 19/101 (18.8%)  G1 (no subtype): 27/101 (26.7%)  G2: 0  G3: 24/101 (23.8%)  G4: 1/101 (1%)  mixed: 1/101 (1%) | Child A: 15/101 (14.8%)  Child B: 67/101 (66.3%)  Child C: 19/101 (18.8%) | SOF/LDV ± RBV 12 wk | 74.3% | No significant differences from baseline  Mortality rate 7.9% (6% Child B, 21% Child C) |
| Aquel *et al*[100], 2015 | G1a: 82/119 (69%)  G1b: 24/119 (20%)  G1 (no subtype): G13/119 (11%) | Child A: 84/119 (70%)  Child B: 34/119 (29%)  Child C: 1/119  (1%) | SMV/SOF ± RBV 12 wk | RVR: 82/119 (69%)  SVR 12: 92/118\* (78%; Child A: 83%  Child B:  68%)  [1 pts died after achieving SVR4] | MELD improvement in 61/92 (66.4%) pts that achieved SVR 12 |
| Saxena *et al*[101], 2015 | 1a: 98/160 (62%)  1b: 62/160 (38%) | Child A: 101/160 (65%)  Child B: 49/160 (31%)  Child C: 6/160 (4%) | SMV/SOF ± RBV 12 wk | Child A (37% with RBV): 91%  Child B/C (35% with RBV): 73% | No significant differences from baseline |

Pts: Patients; LDV: Ledipasvir; SOF: Sofosbuvir; RBV: Ribavirin; DCV: Daclatasvir; SMV: Simeprevir; RVR: Rapid Virological Response (HCV-RNA < 15 UI after 4 wk of treatment); EVR: Early Virological Response (HCV-RNA < 15 UI after 12 wk of treatment); GRZ: Grazoprevir; ELB: Elbasvir; VEL: Velpatasvir; FCH: Fibrosing Cholestatic Hepatitis.

**Table 4 Studies evaluating the effects of direct acting antivirals in liver transplant recipients**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **HCV genotype** | **Fibrosis stage** | **Treatment** | **SVR12 rate** | **Observed improvement** |
| Charlton  *et al*[[9](#_ENREF_91)5] 2015 | Cohort B  G1a: 164/229 (71.6%)  G1b: 63/229 (27.5%)  G4: 2/229 (0.9%) | No cirrhosis: 111/229 (48.5%)  Child A: 51/229 (22.3%)  Child B: 52/229 (22.7%)  Child C: 9/229 (3.9%)  FCH: 6/229 (2.6%) | LDV/SOF + RBV 12 or 24 wk | No cirrhosis:  12 wk 53/55 (96) 24 wk 55/56 (98)  Child A:  -12 wk 25/26 (96%)  -24 wk 24/25 (96%)  Child B:  -12 wk 22/26 (85%)  -24 wk 23/26 (88%)  Child C:  -12 wk 3/5 (60%)  -24 wk 3/4 (75%)  FCH:  -12 and 24 wk 100% | - |
| Manns *et al*[98], 2016 | Cohort B  G1a: 113/226 (50%)  G1b: 86/226 (38%)  G4: 27/226 (12%) | No cirrhosis: 101/226 (44.7%)  Child A: 71/226 (31.4%)  Child B: 40/226 (17.7%)  Child C: 9/226 (4%)  FCH: 5/226 (2.2%) | LDV/SOF + RBV 12 or 24 wk | Genotype 1:  -No cirrhosis: 12 wk: 42/45 (93%)  24 wk: 44/44 (100%)  Child A:  -12 wk: 30/30 (100%)  -24 wk: 27/28 (96%)  Child B:  -12 wk: 19/20 (95%)  -24 wk: 20/20 (100%)  Child C:  -12 wk: ½ (50%)  -24 wk: 4/5 (80%)  FCH:  -12 and 24 wk: 100%  Genotype 4:  No cirrhosis:  -12 and 24 wk 100%  Child A:  -12 wk 3/4 (75%)  -24 wk 100%  Child B:  -12 and 24 wk 100%  Child C:  -12 wk 0% | MELD improved in 58%  Child B to A: 52%  Child C to B: 60% |
| Poordad *et al*[97], 2016 | G1a: 31/53 (58.5%)  G1b: 10/53 (18.9%)  G2: 0  G3: 11/53 (20.7%)  G4: 0  G6: 1/53 (1.9%) | F0:6  F1:10  F2:7  F3:13  F4:16  ND:1 | DCV/SOF + RBV 12 and 24 wk | 50/53 (94%) | - |
| Brown *et al*[108], 2016 | G1a: 87/151 (57.6%)  G1b: 42/151 (27.8%)  G1 (unspecified): 22/151 (14.6%) | Cirrhosis: 97/151 (64.2%) | SMV/SOF ± RBV | 133/151 (88%)  SMV/SOF 105/119 (88%)  SMV/SOF + RBV 28/32 (88%) | - |

LDV: Ledipasvir; SOF: Sofosbuvir; RBV: Ribavirin; DCV: Daclatasvir; SMV: Simeprevir; RVR: Rapid Virological Response (HCV- RNA < 15 UI after 4 wk of treatment); EVR: Early Virological Response (HCV-RNA < 15 UI after 12 wk of treatment); GRZ: Grazoprevir; ELB: Elbasvir; VEL: Velpatasvir; FCH: Fibrosing Cholestatic Hepatitis.