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REVIEW

Hepatitis C virus and liver transplantation: where do we stand?

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Summary

The hepatitis C virus (HCV) infects more than 180 million people globally, with increasing incidence, especially in developing countries. HCV infection frequently progresses to liver cirrhosis leading to liver transplantation or death, and HCV recurrence still constitutes a major challenge for the transplant team. Antiviral therapy is the only available instrument to slow down this process, although its actual impact on liver histology, in responders and nonresponders, is still controversial. We are now facing a "new era" of direct antiviral agents that is already changing the approach to HCV burden both in the pre- and in the post-liver transplantation settings. Available data on sofosbuvir/ledipasvir and sofosbuvir/simeprevir in patients with decompensated cirrhosis sustain a SVR12 of 89% [1], but one-third of patients do not clinically improved. The sofosbuvir/ribavirin treatment in stable cirrhotic patients with HCC before liver transplantation is associated with 2% recurrence rate if liver transplantation is performed at least one month after undetectable HCV-RNA is achieved. The treatment of recurrence with the new antiviral drugs is associated with a SVR that ranges between 60 and 90%. In this review, we have focused on the evolution of antiviral therapy for HCV recurrence from the "old" interferon-based therapy to the "new" interferon-free regimens, highlighting useful information to aid the transplant hepatologist in the clinical practice.

Introduction

Hepatitis C virus (HCV) infection is the leading cause of chronic liver disease and the main indication for liver transplantation (LT) in Europe, North and South America, Australia, and Japan [2]. All patients who undergo LT with detectable serum levels of HCV-RNA experience graft infection, and this constitutes the principal problem for most LT programs worldwide.

HCV recurrence after liver transplantation

Hepatitis C virus recurrent infection after LT is universal, and the natural history of the disease is accelerated compared with the pretransplant setting [2,3]. Within 5 years after LT, histological recurrence is reported in 80% of patients and development of cirrhosis in 30%. Moreover, between 2% and 5% of patients develop a severe form of recurrence termed fibrosing cholestatic hepatitis (FCH), characterized by cholestatic hepatitis and peri-sinusoidal fibrosis, which lead to early graft failure [4]. High replication rates of HCV seem to play a role in FCH. Thus, halting viral replication in this type of recurrence is particularly important [4]. Preventing and managing HCV recurrence represent two of the transplant hepatologist's major challenges. Risk factors for HCV recurrence are related to several factors such as donor and recipient characteristics, aspects related to the

virus, to the surgical act, and to the immunosuppression regimen employed.

Donor factors

Age

Donor age has been confirmed in several studies as the most relevant risk factor for HCV recurrence. A cutoff age that defines an "old" donor as such has not been established yet, and a wide range, between 33 and >70 years, has been used in previous studies and correlated with worse outcome [5]. Furthermore, average donor age has increased meaningfully in the last years, rendering the selection of younger donors for HCV+ recipients very difficult [6].

The match of an older donor and an advanced age recipient is an established predictor of graft failure after LT [7], as well as the match of an older donor and a female recipient [8]. Moreover, the donor–recipient HLA-DRB1 mismatch affects both the occurrence and the progression of HCV infection-related fibrosis [9].

Graft steatosis

It has been suggested that donor graft steatosis might be associated with greater severity of HCV recurrence, development of more accelerated fibrosis progression, and ultimately, poor outcome [10,11]. Nevertheless, other studies have found that mild steatosis of the graft can be safely tolerated in the HCV+ recipient [12,13]. Moreover, the presence of diabetes mellitus in the donor has been identified as an independent risk factor for graft loss in HCV+ recipients compared with HCV- ones [14].

HCV+ donors

The use of HCV+ grafts in HCV+ recipients is not very frequent, but this practice expands the donor pool. In 694 patients with HCV-related cirrhosis who underwent LT, 76 patients (11%) received a graft from anti-HCV+ donors, of whom 63 were matched to recipients of an anti-HCV- donor liver as controls; recurrence of hepatitis C tended to be more rapid in the group of patients who received anti-HCV+ grafts, but this difference did not reach statistical significance [15]. In fact, other studies have shown that in HCV-positive recipients, donor HCV positivity status does not affect graft nor patient survival, nor the rate of HCV recurrence, when compared against the use of grafts from HCV-negative donors [16–20] (Table 1).

Donor-specific alloantibodies

Among donor-related factors associated with HCV recurrence, the study of donor-specific alloantibodies (DSA) is a new field of interest for the transplant community. It has been long believed that the immunological insult to the liver is cellular in nature. Nevertheless, it has been recently reported that DSA classes I and II are independent predictors of fibrosis progression to stages 2–4 and increased risk of death, in patients with HCV recurrence [21].

Split liver

Cases of split liver or living donor liver transplant (LDLT) from HCV- donors have been reported in HCV+ recipients, with no observed difference in terms of fibrosis progression or graft survival [22]. Previous reports have identified LDLT as a risk factor for more severe HCV recurrence compared with deceased donor LT [23–25], possibly due to a greater viral replication [26] associated with hepatocyte regeneration or because of a genetic similarity between donor and recipient, particularly involving HLA matching [27]. In contrast, better results have been reported in more recent series of LDLT, associated with younger donor age and shorter ischemia time [22,28–32].

Donation after cardiac death

The impact of donation after cardiac death (DCD) on HCV recurrence is still controversial. Some reports associate DCD to a more severe HCV recurrence with more rapid disease progression compared with donation after brain death (DBD), with higher rate of graft failure [33]. On the other hand, a matched study did not find any difference in DBD versus DCD regarding fibrosis progression, patient survival, and graft survival [34].

Recipient factors

Diabetes and metabolic syndrome are frequently reported after LT and are related to HCV infection. HCV leads to hyperglycemia and insulin resistance due to a direct alteration of the insulin signaling pathway [35]. Hyperglycemia is associated with HCV disease progression as well as hyperlipidemia and steatosis [36,37]. Likewise, metabolic syndrome is associated with fibrosis progression after 1 year post-LT [38,39].

The negative impact of female gender on HCV recurrence has been recently reported, possibly related to the postmenopausal status being associated with increased steatosis [8] or to a more aggressive virological disease [40].

The HIV–HCV coinfection is associated with higher progression rate to severe fibrosis and a lower survival rate compared with monoinfected patients, but the survival benefit after LT is satisfactory for these patients [41,42]. Moreover, in HIV/HCV-coinfected patients a higher rate of FCH has been reported, and therefore, a strict follow-up and early administration of antiviral therapy (AT) is mandatory [43].

CMV and HHV6 reactivation have been correlated with a greater severity of HCV recurrence; however, it is not

Table 1. Patient survival in HCV-positive recipients of organs from HCV-positive donors.

Author [Ref]	N transplant (HCV + donor/ HCV+ recipient)	Control group (HCV – donor/ HCV + recipient)	1-, 5-, and 10-year patient survival	*P*
Ballarin *et al.* [15]	76	Yes (63 pts)	1 year: 83.6% vs. 95.1% 5 year: 61.7% vs. 68.2%	0.22/0.11
Saab *et al.* [20]	59	Yes (59 pts)	1 year: 76% vs. 88% 5 year: 64% vs./60%	0.14
Burr *et al.* [17]	540	Yes (540)	n.a.	0.57 (matched cohorts)
Montenovo [18]	1433	Yes (21884)	1 year: 83% vs. 58% 5 year: 63% vs. 62% 10 year: 46% vs. 40%	NS
Alvaro *et al.* [16]	13	130	1 year: 91.7% vs. 82.7% 5 year: 81.5% vs. 65.8%	0.25

clear whether CMV and HHV6 can be considered as independent risk factors or just markers of over-immunosuppression [44].

The presence in both the recipient and the donor of the interleukin-28B (IL-28B) polymorphism in the gene region, which encodes for interferon (IFN)-lambda3, is strongly predictive of HCV recurrence [45]. Genotype TT of polymorphism rs12979860 is associated with more rapid fibrosis progression. The relationship between recipient IL-28B genotype and the time-to-recurrence of hepatitis C infection has been shown, however, to be independent from the donor IL-28B genotype [46]. This was confirmed by the finding that recipient IL-28B CC genotype is associated with lower alanine aminotransferase levels and viral load at recurrence and a lower frequency of fibrosis ≥2 on liver biopsy at 1 year after LT, when compared with the non-CC genotype. The opposite has been observed in LT recipients of CC genotype donors [47]. The non-CC genotype also seems to be associated with the more aggressive form of HCV recurrence: FCH [48]. Moreover, the IL-28B rs12979860 CC and rs8099917 TT genotypes have been proven to be predictors of PEG-IFN/ribavirin (RBV)-treated HCV recurrence [49]. Particularly, recent studies support the possibility that the genetic variants associated with favorable interferon response are associated with higher inflammatory activity and hence higher fibrosis progression [50,51].

Virological factors

Serum HCV-RNA decreases rapidly after the removal of the infected liver and during the implantation of the new graft. In the first week after the LT, viral kinetics appear highly variable among individuals [52]. However, Fukumoto *et al.* [53] showed that the liver graft is rapidly reinfected by HCV after LT. Thereafter, the new liver becomes infected and serum HCV-RNA reaches or even exceeds levels before LT [54]. The impact of the viral load on the clinical outcome is still controversial, however. From some studies, it seems associated with fibrosis development at 1 year after LT [55] and increased mortality [56]. The influence of HCV genotype is debatable, as it has been reported that genotype 1b is associated with more severe recurrence [57,58] [2], but it has also been reported that the genotype appears to have no influence on viral recurrence [59].

Factors related to the transplant

Ischemia–reperfusion injury, which depends on several peri-operative factors such as cold and warm ischemia time, preservation solution and technical factors during graft removal, donor status (DCD/DBD), and type of reperfusion, contributes to increase in morbidity and mortality after LT. In particular, it has been observed that in HCV + recipients, early preservation injury on biopsy is associated with progression to stages 3–4 of fibrosis and poorer survival rates compared with HCV-infected patients without preservation injury or HCV-infected patients with preservation injury [60]. Biliary complications after LT are diagnosed more frequently in HCV + patients, but HCV recurrence itself, rather than this complication, is correlated with poor outcome of the graft [61].

Immunosuppression

Immunosuppression is one of the key factors for HCV disease progression after LT [62].

Pulsed intravenous methylprednisolone treatment for acute cellular rejection is associated with transient increases in HCV-RNA levels [54], and with a more rapid disease progression [63]. On the contrary, the slow tapering of steroids seems to reduce HCV progression [63,64].

Complete steroid avoidance has not been correlated with a reduction in HCV recurrence or an improvement in patient or graft survival, although this regimen is safe and effective, as demonstrated by two multicenter randomized trials [65–67].

Cyclosporine (CsA) has an antiviral effect on HCV *in vitro* [68–70] that has, however, never been confirmed *in vivo*. Nevertheless, a recent study found that CsA in steroid-free regimens is associated with less fibrosis at 1 year after LT [71]. CsA was preferred in the past as it was associated with higher sustained virological response (SVR) rates when patients were treated with peg-IFN and RBV; this association has not been yet confirmed for the new-generation antivirals. In calcineurin inhibitors (CNIs) and steroids regimen, no difference between the two CNIs has been found [67]. Yet, tacrolimus has been preferred in recent years because of its association with a better survival [72].

The impact of azathioprine (AZA) and mycophenolate mofetil (MMF) is still controversial. Some studies have reported an association between MMF and HCV increased severity [73], while others have observed the stabilization of disease, and yet in other studies, worsening has been noted. Similarly, AZA seems to have a beneficial effect [62]. The above data do not allow for any recommendation to be made regarding the choice of immunosuppression in this scenario.

In summary, all previously mentioned risk factors for HCV recurrence and disease progression reported in the era of Peg-IFN/RBV treatment should still be considered. However, the scenario is deeply changing in this new era, as several patients will be successfully treated before LT or early after LT, and the risk factors related to the donor and the recipient, as well as viral-related factors, will probably have a lesser impact on the development and progression of fibrosis. Of course, it is too early to draw definitive conclusions on the impact of the new drugs on the overall management of HCV+ recipients, as data are still needed on relapse after treatment with the new DAAs, and the best re-treatment schedule in those cases. This means that the issue why fibrosis progression is more rapid in some patients after liver transplantation but not in others still remains an open one.

Moreover, the actual impact on the status of patients on the waiting list is yet to be seen, and future studies will demonstrate whether improvement is such to allow for patient de-listing. Caution is warranted in these cases, until more data become available; it might be advisable to temporarily suspend from the waiting list those patients in whom improvement on therapy is observed, rather than to remove them altogether from the list. An interesting case has been recently reported, concerning a 67-year-old woman who was listed for LT for decompensated cirrhosis (CTP 12, MELD 16), refractory ascites, and chronic encephalopathy. After successful treatment with sofosbuvir and ribavirin and SVR12, liver function and clinical status improvement allowed for her to be removed from the liver transplant waiting list. [74].

Retransplant

Survival of HCV+ LT recipients is significantly lower compared with patients transplanted for other indications [75], and whether to re-transplant or not LT recipients with decompensated HCV cirrhosis remains a relevant and much debated issue, as patient survival and graft survival are lower after re-LT compared with the first transplant [76,77].

Moreover, most deaths after re-LT are related to postoperative complications, especially sepsis [78,79].

Some studies have suggested that HCV infection is a risk factor for mortality [80–82]; however, on multivariate analysis, other variables such as recipient age, model for end-stage liver disease (MELD) >25, re-LT during the first year after LT, donor age >60, and a warm ischemia time ≥75 min have emerged as independent predictors of mortality. On the other hand, the association between HCV and mortality risk has been clearly demonstrated in other studies, with HCV-infected recipients having a 30% higher risk of mortality than those without HCV infection [83].

The International Liver Transplantation Society Expert Panel established that bilirubin >10 mg/dl, creatinine >2.0 mg/dl (or creatinine clearance <40 ml/min), recipient age >55, donor age >40, and early HCV recurrence (cirrhosis <1 year after LT) are variables associated with a worse outcome after RT [84]. Other important factors include HCV status, recipient age, donor age, warm and cold ischemia times, UNOS status (ICU, hospital ward, ambulatory), mechanical ventilator support, and interval to retransplantation. Postretransplantation survival rates are higher with younger recipients, longer intervals between transplants (>2 months), and retransplantation before severe decompensation [85,86].

The use of a prognostic score would be helpful for deciding who would benefit from re-LT avoiding futile transplantation [85].

Interestingly, multiple transplants can safely be performed [87]. Nevertheless, taking into account organ shortage and costs related to the procedure, it becomes mandatory to prevent the need for re-LT by achieving viral clearance and halting disease progression.

Unfortunately, there are only few models reporting data on futility after re-transplantation [88].

As previously reported, several mathematical models have been developed to predict survival after retransplantation using multivariate regression analysis [84–86]. The most significant challenges to further improvement in the accuracy of these models include the inability to model random operative and perioperative events that are by definition unpredictable. Additionally, as the vast majority of these models were developed on patients that already had undergone retransplantation, and not in patients being

selected for retransplant, a selection bias may limit the wider application to clinical decision-making [88].

It is hoped that although there are no data published yet, in the near future, the new antivirals will expectedly reduce the need for re-transplantation due to recurrence of hepatitis C.

Fibrosis progression after liver transplantation: Is better knowledge of cellular and histological findings needed?

Fibrosis progression is not linear and may vary according to different time points after LT [89]. Serial liver biopsies have shown that the histological activity at HCV recurrence diagnosis predicts the risk of cirrhosis development [90]. However, in recent years, recipients have reportedly higher fibrosis rate compared with the past, for similar grading scores [91]. This finding suggests that other factors may be responsible for the increase in liver fibrosis.

Fibrosis progression in HCV transplant recipients is associated with early activation of hepatic stellate cells (HSC), a process that appears to be partially independent from necro-inflammatory activity [92].

Moreover, telomere shortening exhausts the hepatocyte's ability to replicate and fosters fibrogenesis. Similar to the telomere model, a stress-induced model of p21-mediated hepatocyte mito-inhibition emphasizes the importance of a replicative disadvantage for hepatocytes [93]. Nevertheless, an important difference is that hepatocyte inhibition is potentially reversible if stressors are minimized or eliminated. This model explains why any stress to hepatocytes, such as steatosis, iron, inflammation, HCV+ replication, and spontaneous increase in p21 expression associated with aging, can accelerate fibrosis progression [94].

To control fibrosis progression, AT is administered in patients with HCV recurrence. Although the evaluation of AT response is often based more on virology than on histology, it has been reported that IFN may play an antifibrotic effect even in those patients in whom an antiviral effect is not observed [95]. Moreover, AT seems to slow down disease progression in SVR [96] and increases patient survival in treated LT recipients [97–99]. Table 2 summarizes data on post-treatment fibrosis modification [96,100–114].

Antiviral therapy for HCV recurrence: the past

Combined peg-IFN and weight-based RBV was the standard-of-care treatment for patients with established HCV recurrence after LT.

Ribavirin should be dosed not only according to body weight but also according to kidney function (GFR). For this reason, tolerability of full-dose RBV (i.e., 1000/1200 mg) is limited in the majority of LT patients and results in high rates of severe anemia, determining the need for a lower initial dose in many studies [115].

When to start AT has been always a controversial subject.

Pre-emptive AT, defined as therapy started quite early after OLT (<12 weeks), and before histological disease recurrence is present, is currently not recommended, as the efficacy has been demonstrated by several studies to be rather poor [116–118]. The pre-emptive strategy, however, might eventually be used with the new-generation antivirals, as they are better tolerated compared with Peg-IFN.

Carrión *et al.* randomized patients with mild recurrent hepatitis C (fibrosis stages F0 to F2) to either no therapy or treatment with peg-IFN-α-2b and RBV for 48 weeks. When the group of patients who received early treatment was compared against those who were treated only after a worsening fibrosis score (F3 to F4), their fibrosis progressed by at least one stage in 26% of cases compared with 54%, respectively [96].

In the study by Berenguer *et al.*, the efficacy (EVR, EOT, SVR) of AT was compared between two noncontemporaneous cohorts of post-LT naïve patients treated with pIFN-RBV: group 1 ($n = 44$, F4 20.5%) and group 2 ($n = 70$, F4 7%) ($P = 0.035$). Patients of group 2 in whom treatment was started as soon as there was evidence of mild fibrosis showed an increase in SVR in comparison with patient of cohorts B (from 25% to 54%) ($P = 0.002$) [119,120].

Concerning fibrosing cholestatic hepatitis, a review analyzed 16 studies including 42 patients, of whom 13 experienced a virological and biochemical response, three underwent re-LT, 19 died, and the outcome was not reported for seven patients [120].

Therapy duration is still an open issue; the recommended duration of treatment for all genotypes is 48 weeks, except for genotype 1 patients who do not achieve a negative HCV-RNA at week 4 and a decrease of more than two log in HCV-RNA at week 12. In these cases, the extension of the treatment to 72 weeks is still debatable, as no randomized studies to support this policy have been yet published. Patients with genotype 2 or 3, low viral load (<400 000 U/ml), mild fibrosis, and those in whom HCV-RNA becomes undetectable in 4 weeks (i.e., RVR) may need only 24 weeks of therapy, but this can increase the relapse rate [121]. These same authors have proposed long-term AT for patients who have not responded after 48 weeks of treatment [122,123].

Regarding side effects of AT, the most common are neutropenia and anemia, which can be treated with the administration of growth factors such as granulocyte colony-stimulating factors and erythropoietin. Several immunological derangements such as acute cellular rejection, chronic ductopenic rejection, and autoimmune-type

Table 2. Changes in necro-inflammatory grade and fibrosis stage in HCV-infected liver transplant recipients treated with interferon-based therapy.

Author; [Ref]	*N* treated	SVR *n* (%)	Changes in fibrosis	Changes in activity
Rodriguez-Luna *et al.* [112]	19	5 (26)	SVR: Improvement in 60% No change in 20%, Worsening in 20%	SVR: improvement in 100% NR: improvement in 40%
Neff *et al.* [108]	57	8 (14)	39 patients with paired biopsies: Improvement in (18) No change in (10) Worsening in (11)	n.a.
Ross *et al.* [113]	16	0 (0)	Nine patients with paired biopsies: No change in (2) Worsening in (7)	n.a.
Dumortier *et al.* [103]	20	9 (45)	2.2–1.6	1.8–0.3
Toniutto *et al.* [114]	12	1 (8)	No change in 6 (50%)	No change in 3 (25%)
Biselli *et al.* [102]	20	9 (45)	Improvement in 4/9	
Berenguer *et al.* [101]	67	22 (33)	38 patients with paired biopsies: SVR (n = 10) Improvement in (2) No change in(4) Worsening in (4) NR (n = 28) Improvement in (4) No change in (13) Worsening in (11)	SVR (n = 10) Improvement in (6) No change in (3) Worsening in (1) NR (n = 28) Improvement in (10) No change in (10) Worsening in (8)
Oton *et al.* [110]	55	24 (44)	15 patients with paired biopsies: SVR: 2.4 ± 1.9–2.6 ± 1.3 NR: 2.7 ± 1.7–3.7 ± 1.6	SVR: HAI: 7.5 ± 2.1–3.3 ± 2.8 NR: HAI: 7.1 ± 1.1–5.3 ± 3.2
Mukherjee *et al.* [116]	32	11 (34.3)	15 patients with paired biopsies: Improvement in(1) No change in (6) Worsening in (8)	n.a.
Mukherjee *et al.* [107]	39	13 (33.3)	Improvement in (4) No change in (10) Worsening in (3)	n.a.
Fernandez *et al.* [104]	47	11 (23)	16 patients with paired biopsies: SVR (n = 7): 1.5 ± 1.1–1.16 ± 1.0 NR (n = 9): 2.4–2.8	SVR PI: 2.3 ± 0.7–1.3 ± 0.7 LI: 2.8 ± 0.7–0.8 ± 0.9 NR No change in HAI PI: 2.2-2.4 LI: 2.3-2.1
Neumann *et al.* [109]	25	9 (36)	1.7–2.0	1.66–1.13
Angelico *et al.* [100]	21	7 (33)	10 patients with paired biopsies: Improvement in (2) Worsening in (7)	Improvement in (2/10) Worsening in (2/10)
Carrion *et al.* [96]	54	18 (33)	Improvement in (11) No change in (22) Worsening in (21)	n.a.
Hanouneh *et al.* [105]	53	19 (35)	18 patients with paired biopsies: 2 (1–2) to 2.5 (1–3)	Unchanged
Roche *et al.* [111]	113	54 (38)	81 patients with paired biopsies: SVR (n = 42): 2.3 ± 1.0–2.2 ± 1.3 Improvement in (11) No change in (22) Worsening in (9) NR (n = 39): 2.0 ± 0.9–2.4 ± 1.0 No change in (18) Worsening in (17)	SVR: 1.9 ± 0.6–1.0 ± 0.6 NR: 1.9 ± 0.7–1.4 ± 0.6

SVR, sustained viral response; NR, nonresponse; HAI, hepatic activity index; LI, lobular inflammation; PI, portal inflammation; n.a., not available.

graft hepatitis have been reported [124] in relation to AT. With combination therapy, the risk is below 10%, and controlled studies have revealed no differences in acute rejection rates between treated patients and untreated controls.

A country-based experience [125] reported the results obtained after treatment with standard AT after LT. From this Italian database, patients in whom liver biopsy was performed at least once before and once after completion of therapy were selected for analysis. Both per-protocol biopsies (from the majority of participating centers) and nonprotocol biopsies were included in the study.

The cohort of antiviral-treated patients was followed to assess the impact of AT on fibrosis progression. In this retrospective analysis, patients underwent liver biopsy at 12-24 months (T 12-24), 36 months (T 36), and 60 months (T 60) after the end of AT.

The expert pathologist of each LT center assessed the hepatic inflammation (grade-G) and fibrosis (stage-S) according to the Ishak score of 100.

Fibrosis, compared among the pretreatment biopsy and the biopsies at different time points after AT, was defined as "improved" if there was a loss of at least 2 stages, "stable" if there was no change, and "worsened" if there was an increase of at least 2 stages.

Fibrosis change in SVR+ vs. SVR– patients comparing pretreatment biopsy with post-treatment biopsy and with the last available biopsy was evaluated, and risk factors for fibrosis progression were assessed.

Overall, 180 liver biopsies were performed in 200 patients, 102 at T 12-24, 52 at T 36, and 26 at T 60. Comparing pretreatment with post-treatment biopsy in SVR+ vs. SVR- patients, worsening of fibrosis was seen in 8 (12%) vs. 25 (19%) ($P = 0.2238$). In SVR+ patients, no variables were significantly associated with worsening of fibrosis. In SVR- patients, fibrosis stabilization/improvement was associated with younger donor age ($P = 0.0237$) and a shorter time interval between LT and AT ($P = 0.0130$). Comparing pretreatment with last biopsy in SVR+ vs. SVR- patients, fibrosis worsening was seen in 11 (16%) vs. 49 (38%) ($P = 0.0011$). In SVR+ patients, worsening of fibrosis was associated with older donor age ($P = 0.0091$). In SVR- patients, fibrosis stabilization/improvement was associated with younger donor age ($P = 0.0129$) and lower fibrosis stage at pretreatment biopsy ($P = 0.0520$).

In this series of patients, risk factors that correlated with fibrosis progression at post-treatment biopsy after multivariate analysis were as follows: older donor ($P = 0.015$), pretreatment biopsy higher fibrosis stage ($P < 0.0001$); at T 12-24: diabetes ($P = 0.0279$), older donor ($P = 0.0023$), and pretreatment biopsy higher fibrosis stage ($P = 0.0043$); at T 36: female recipient gender ($P = 0.0450$) and pretreatment biopsy higher fibrosis stage ($P = 0.0126$).

The importance of pretreatment biopsy-proven fibrosis has been previously reported: Roche *et al.* found that fibrosis stage ≥3 before AT is associated with less tolerability (graft or patient failure) compared with fibrosis <3 [111]. Moreover, Carrion *et al.* observed that variables associated with histological improvement/stabilization were mild vs. severe HCV recurrence and AT vs. no treatment [96].

The association of IFN plus RBV with first-generation protease inhibitors, boceprevir (BOC) and telaprevir (TVR), has been correlated with a higher SVR but with severe side effects such as anemia for boceprevir and skin rash for telaprevir [126]. Particularly, Coilly *et al.* [126] reported results on a multicenter study on 37 patients treated with triple therapy (TVR $n = 19$, BOC $n = 18$) after LT. This study included difficult-to-treat patients with advanced fibrosis (83% with fibrosis stage ≥ 2) as well as nonresponders to a previous course of standard therapy, post-LT patients, and CH patients (16%). A RVR was obtained in 19/37 patients (51%) (BOC: 56%; TVR: 47%) at week 4 of triple therapy. A complete EVR was achieved in 27 patients (73%) (BOC: 89%; TVR: 58%), and an end of treatment response was observed in 28 patients (76%) (BOC: 72%; TVR: 40%). Finally, a SVR12 was obtained in one of the five eligible patients (20%) in the TVR group and five of the seven eligible patients (71%) in the BOC group. Pungpapong *et al.* reported the results in three centers that used BOC ($n = 25$) and TVR ($n = 35$) in 60 patients with fibrosis stage ≥2 for a follow-up of 66 weeks (mean = 35 weeks). At week 4 of PI therapy, HCV-RNA was undetectable (RVR) in six (17%) and six patients (24%) in the TVR and BOC groups, respectively. At week 12 of therapy, HCV-RNA was undetectable (EVR) in 28 (80%) and 10 patients (40%) in the TVR and BOC groups, respectively. Three patients (at week 18, 20, and 22) and one patient (at week 19) developed viral breakthrough in the TVR and BOC groups, respectively [127]. Tolerance to antiviral triple therapy is a major issue in liver transplant patients. Pungpapong *et al.* reported seven cases of infection (six in the TVR group, one in the BOC group). Two patients died and three patients with pretreatment cirrhosis developed hepatic decompensation. In the series described by Coilly *et al.*, there were 10 infections and three patients died. For these reasons, the use of this combination therapy is no longer recommended after LT. The most important differences between past and present treatment of HCV infection are showed in Table 3 [128].

New antiviral strategies

Interferon-free combinations are rapidly taking over, as they are associated with better response rates, a shorter treatment duration, and milder side effects.

Table 3. Differences between PEG-interferon-based regimens and DAAs.

	PEG-interferon-based regimens	DAAs
Mechanism of action	Immune based. Direct and indirect suppression of HCV replication	Inhibition of specific virus enzymes
Duration	Long-term therapy	Short(er)-term therapy
Administration	Subcutaneously	Oral
Influence of HCV genotype	Relevant, GT-2 and GT-3 are more sensitive than GT-1	Sofosbuvir: all HCV genotypes (GT3 is less sensitive than others) Daclatasvir, ledipasvir, ABT267: all HCV genotypes Simeprevir, asunaprevir, faldaprevir, ABT450/ABT333: GT1B>GT1A
Predictor of response to antiviral therapy	Evaluated before therapy	No need to be evaluated before therapy
Tolerability	Significant adverse events	Well tolerated
Major side effects	Constitutional syndrome, hematologic complications (neutropenia, anemia) neuropsychiatric, nausea, rash, and cough	Sofosbuvir: headache, fatigue, Daclatasvir, ledipasvir, ABT267, ABT333: rash Simeprevir, asunaprevir, faldaprevir, ABT450/ABT333: nausea, rash
Hematologic toxicity	Frequent	Rare
Need of support therapy	Frequent	Rare
Efficacy	SVR range from 20 to 40%, depending on patient characteristics	SVR ranging from 80 to 95%, also in "difficult-to treat" populations
Decompensated liver disease	Contraindicated	Patients with decompensated cirrhosis (Child–Pugh B and Child–Pugh C, up to 12 points) and without concomitant comorbidities that could impact their survival can be treated with the combination of sofosbuvir and ribavirin for 16-20 weeks (genotype 2), the fixed-dose combination of sofosbuvir and ledipasvir (genotypes 1, 4, 5, and 6), or the combination of sofosbuvir and daclatasvir (all genotypes), with weight-based ribavirin, for 12 weeks [128] Patients with decompensated cirrhosis with contraindications to the use of ribavirin or with poor tolerance to ribavirin on treatment should receive the fixed-dose combination of sofosbuvir and ledipasvir (genotypes 1, 4, 5, or 6), or the combination of sofosbuvir and daclatasvir (all genotypes) for 24 weeks without ribavirin [128]
Drug–drug interactions	Induction of CYP2D6 and CYP2C8/9 (caution with warfarin, phenytoin (CYP2C9), and flecainide (CYP2D6))	Should always be considered The efficacy and toxicity of concurrent drugs and potential drug–drug interactions should be monitored during treatment When possible, an interacting co-medication should be stopped for the duration of HCV treatment or the interacting co-medication should be switched to an alternative drug with less interaction potential
Patients with renal failure		Simeprevir, daclatasvir, and the combination of ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir are cleared by hepatic metabolism and can be used in patients with severe renal disease Sofosbuvir should not be administered to patients with an eGFR <30 ml/min/1.73 m2 or with end-stage renal disease until more data are available
Stopping (futility) rules	Yes, depending on drug type	With the triple combination of Peg-IFN-α, ribavirin, and simeprevir, treatment should be stopped if HCV-RNA level is ≥25 IU/ml at treatment week 4, week 12, or week 24 No futility rules have been defined for other treatment regimens

Introduced in the clinical practice for compassionate use, some of the new antiviral agents have now been approved at the European board and some others will be soon approved. In 2014, four drugs were approved: sofosbuvir (SOF), simeprevir (SMV), daclatasvir (DAC), and ledipasvir (LDV). In January 2015, a new combination including paritaprevir, ombitasvir, and dasabuvir was also approved. SOF is an HCV NS5B nucleotide polymerase inhibitor and is a pro-drug [129]. It is administered at the dose of 400 mg once daily, and no dosage adjustments are required for mild or moderate renal impairment (CrCl ≥30 ml/min), but safety and efficacy have not been established in patients with severe renal impairment (CrCl <30 ml/min) or end-stage renal disease requiring

hemodialysis [130]. However, recent data suggest its use might be safe in patients with chronic kidney disease [131]. Major side effects are fatigue, headache, nausea, insomnia, and anemia. SMV is an HCV NS3/4A protease inhibitor. It is administered at the dose of 150 mg once daily, and no data about dose adjustment in patients with Child–Pugh B or C cirrhosis are available yet. As it is metabolized by CYP3A, the co-administration of SMV with drug inducers or inhibitors of CYP3A is not recommended, as they lower or increase SMV exposure, leading to necessary dose adjustments [132]. Concomitant use of cyclosporine resulted in significantly increased plasma concentrations of simeprevir; thus, cyclosporine co-administration is not recommended. Concomitant use with sirolimus may result in mildly increased or decreased plasma concentrations of sirolimus. Routine monitoring of blood concentrations of sirolimus is therefore recommended. DAC is administered at the dose of 60 mg once daily. It is a substrate of CYP3A, and substrate and inhibitor of P-gp. The dose of DAC must be adjusted to 30 mg daily in HIV-infected patients receiving atazanavir/ritonavir, and to 90 mg daily in those receiving efavirenz. LDV is an inhibitor of the HCV NS4A protein. It is administered once daily in combination with SOF (90 mg/400 mg) in one pill. Dose adjustment is recommended for patients with mild to moderate renal impairment, while there are insufficient data in patients with end-stage renal disease or in dialysis. Ledipasvir–sofosbuvir has significant drug–drug interactions with P-gp inducers, and the co-administration is not recommended [130]. In details, induction of P-gp by anti-epileptic drug (phenytoin, phenobarbital, carbamazepine, and oxcarbamazepine) or by antibiotics (rifampin, rifabutin, and rifapentine) results in reduction of ledipasvir bioavailability. Moreover, in patients taking proton pump inhibitors, it is important to administer these drugs after intake of ledipasvir–sofosbuvir [130]. Sofosbuvir appears to have the lowest potential for drug interactions because it lacks involvement with the CYP450 enzyme system and has no identified inhibitory effects on transporter proteins; however, as ledipasvir is coformulated with sofosbuvir, all drug interactions pertaining to sofosbuvir need to be considered as well. Paritaprevir (ABT-450) is a protease inhibitor that interferes with the HCV proteins NS3/4A and is administered once daily (150 mg) with a small dose (100 mg) of another drug called ritonavir (Norvir). The purpose of the small dose of ritonavir is to boost and maintain levels of ABT-450 in the blood. Ritonavir does not have activity against HCV and has only minimal activity against HIV at such a low dose. Ombitasvir (ABT-267) is an inhibitor of the NS5A and is administered once daily (25 mg). The three drugs (paritaprevir/ritonavir and ombitasvir) are administered together. Medicinal products that are highly dependent on CYP3A for clearance, and for which elevated plasma levels are associated with serious events, must not be co-administered, or plasmatic drug levels should be strictly monitored. Dasabuvir (ABT-333) is a non-nucleoside polymerase inhibitor and is taken twice daily (250 mg). Co-administration with medicinal products that are strong or moderate enzyme inducers is expected to decrease dasabuvir plasma concentrations and reduce its therapeutic effect. Moreover, medicinal products that are strong CYP2C8 inhibitors may increase dasabuvir plasma concentrations. Interestingly, in patients with renal severe dysfunction, paritaprevir/ombitasvir and dasabuvir may be given to patients with GFR >15 ml/min [130]. The prescription of a combination of the new drugs takes into account the viral genotype, the response to a previous viral therapy, the stage of liver disease, and drug–drug interactions, especially for HIV-coinfected patients and liver transplant recipients.

Antiviral therapy before liver transplantation

Treating the patient before LT has a great impact on transplant outcome, as in the presence of negative viral load at the time of LT, there is little chance of virus reactivation after LT. Nevertheless, patients awaiting LT are a challenging population to treat; IFN is contraindicated in decompensated cirrhosis, and previous experience of BOC and TVR administered to patients with cirrhosis resulted in the occurrence of important side effects for a small benefit. In the Compassionate Use of Protease Inhibitors in Viral C Cirrhosis study, 511 patients with HCV genotype 1 infection and compensated cirrhosis who did not respond to a prior course of Peg-IFN and RBV (44.3% relapsers or patients with viral breakthrough, 44.8% partial responders, and 8.0% null responders) were given either TVR (n = 299) or BOC (n = 212) for 48 weeks. Among patients given TVR, 74.2% of relapsers, 40.0% of partial responders, and 19.4% of null responders achieved SVR12. Among those given BOC, 53.9% of relapsers, 38.3% of partial responders, and none of the null responders achieved SVR12. On multivariate analysis, factors associated with SVR12 included prior response to treatment response, no lead-in phase, HCV subtype 1b (vs. 1a), and baseline platelet count >100 000/mm^3. Severe adverse events occurred in 49.9% of cases, including liver decompensation, severe infections in 10.4%, and death in 2.2%. On multivariate analysis, baseline serum albumin level <35 g/l and baseline platelet counts of 100 000/mm^3 or less predicted severe side effects or death [133]. Moreover, the use of ribavirin is associated with high rates of anemia, especially in patients with advanced liver disease [127]. With this as the starting point, it seems that the IFN-free regimens will be the treatment of choice before and after LT.

As antiviral treatment before LT can prevent HCV recurrence, but existing IFN-based regimens are poorly tolerated and are either ineffective or contraindicated in most patients, a trial to determine whether SOF and RBV treatment before LT could prevent HCV recurrence after LT was recently performed. In this phase 2, open-label study, 61 patients with HCV of any genotype and cirrhosis (Child–Turcotte–Pugh score, ≤7) who were on the waiting list for LT for hepatocellular carcinoma received up to 48 weeks of SOF and RBV before LT [134]. The primary end point was the proportion of patients with HCV-RNA levels <25 UI/ml at 12 weeks after LT among patients with this HCV-RNA level at their last determination before LT. Sixty-one patients received SOF and RBV, and 46 underwent liver transplantation. The per-protocol efficacy population consisted of 43 patients who had HCV-RNA level <25 IU/ml at the time of LT. Of these 43 patients, 30 (70%) had a post-LT virological response at 12 weeks, 10 (23%) had recurrent infection, and 3 (7%) died (two from primary graft nonfunction and one from complications related to hepatic artery thrombosis). Of all 61 patients given SOF and RBV, 49% had a post-LT virological response. Recurrence was related inversely to the number of consecutive days of undetectable HCV-RNA before LT. The most frequently reported adverse events were fatigue (in 38% of patients), headache (23%), and anemia (21%). Therefore, the authors conclude that the administration of SOF and RBV before LT is safe and well tolerated and can prevent post-transplant HCV recurrence.

In a recent report, the combination of SOF and SMV ± RBV was administered for 12 weeks in patients with advanced liver disease. Of the 91 patients, 82.4% had cirrhosis and of those, 36% were listed for LT. In an intention-to-treat analysis, the SVR12 was significantly higher for patients without cirrhosis (100%) compared with patients with cirrhosis (81%) ($P < 0.05$). No difference in SVR12 according to Child A or B, and no difference according to the use of RBV (87% versus 85%), was observed. No difference was identified in previously treated patients (84%) compared with naïve patients (85%), and even though patients infected with genotype 1b did slightly better (85%) than those infected with genotype 1a (88%), the difference was not statistically significant [135].

A small cohort of 25 patients with decompensated cirrhosis (CTP≥7) were started on SMV + SOF + RBV (18 with ascites and 16 with esophageal varices). Of note, all 25 (100%) patients achieved RVR and EOT. Moreover, no further decompensation during treatment and no severe adverse effects (no need of blood transfusion) were observed [136].

A phase II, randomized, prospective, multicenter trial, using fixed-dose combination of SOF+LDV plus RBV for 12 or 24 weeks in treatment-naïve and treatment-experienced patients with GT1 or four and decompensated liver disease who were awaiting LT, was reported. The exclusion criteria were as follows: Child–Pugh scores from 13 to 15; history of major organ transplant, including liver; presence of HCC; total bilirubin ≥10 mg/dl; hemoglobin ≤10 g/dl; creatine clearance ≤40 ml/min; and platelets ≤30 000 [1].

Fifty-three patients were treated for 12 weeks, including 30 CTP B and 23 CTP C patients, while 55 patients were treated for 24 weeks, including 29 CTP B and 26 CTP C patients. Patients were predominantly male (67%), Caucasian (93%), and had been previously treated for HCV (65%). Mean baseline HCV-RNA was 5.8 log10 IU/ml range 3.2–7.1 log10 IU/ml. Twenty-eight patients (26%) had a MELD score >15. At baseline, 96% of CPT class C patients had ascites and 88–91% encephalopathy, in the 12- and 24-week arms, respectively.

Overall, the SVR12 was 87% and 89% for the patients treated for 12 and 24 weeks, respectively. No significant difference was observed for the CTP B patients (87% vs. 89%) or for the CTP C patients (86% vs. 90%), but the number of patients is limited.

The other very important observation from this trial was the quite drastic clinical improvement of the patients with successful HCV therapy, which was documented by an improvement in MELD score as well as an increase in serum albumin, all indicative of an improvement of hepatic synthetic function. Nevertheless, the condition of some patients stabilized, while it worsened in other patients, meaning that cirrhosis was already too advanced to improve despite viral clearance. The impact of the RBV was not tested.

Therapy duration and the benefit of RBV are still controversial, and no data are available to make recommendations in this respect.

An interesting case has been recently reported, concerning a 67-year-old woman who was listed for LT for decompensated cirrhosis (CTP 12, MELD 16), refractory ascites, and chronic encephalopathy. After successful treatment with sofosbuvir and ribavirin and SVR12, liver function and clinical status improvement allowed for her to be removed from the liver transplant waiting list [74]. Nowadays criteria for de-listing patients have not been identified yet, and a successful treatment before LT is not always correlated with a clinical and biological improvement. Patients with high MELD scores (the patient of the case report has only MELD 16) will probably obtain less benefit from a viral clearance.

Safety and efficacy of all oral anti-HCV drugs in patients with decompensated cirrhosis (MELD score of ≥10) participating in the ongoing multicenter study HCV-TARGET were recently presented [137]. Among 277 patients [mean age: 59 years, 69% male, mean MELD score: 13 with range

from 10 to 28] of whom 58.5% had failed prior AT and 9.7% had failed prior TLV/BOC triple therapy, SVR4 rates in those with available data were as follows: SOF/RBV (GT2) in 18/24 patients (75%), SOF/SIM (GT1) in 55/71 patients (77%), and SOF/SIM/RBV (GT1) in 13/16 patients (81%). At least one AE was reported by 88% of patients, although most events were mild. Among patients with available pre/post-treatment data, bilirubin improved in 46/58 patients (80%), albumin improved in 33/54 patients (61%), but in 10/58 (17%) and 14/54 (26%), bilirubin and albumin worsened, respectively, which open the discussion on the need in such patients for priority more than de-listing patients with SVR.

Administration of LDV/SOF+RBV in patients with decompensated cirrhosis has been evaluated in United States (SOLAR 1) and Europe, Canada, Australia, and New Zealand (SOLAR 2), the largest study of such patients to be evaluated to date [138]. Among patients with Child B, liver cirrhosis SVR4 was observed in 24/28 patients (86%) and 11/11 patients (100%) in 12 and 24 weeks arms, respectively. A total of 14/16 (88%) and 3/6 (50%) Child C patients achieved SVR4 in 12 and 24 arms, respectively. In the same cohort, the drug safety was evaluated. Among 215 patients with liver cirrhosis (117 Child B and 98 Child C), only 22 (Child B) and 35 (Child C) experienced serious adverse events, mainly anemia due to RBV. An algorithm for the management of patients with HCV-related liver cirrhosis awaiting liver transplantation is resumed in Figure 1.

Antiviral therapy after liver transplantation

All patients with HCV recurrence after LT should be considered for AT. However, drug–drug interactions are particularly important in LT recipients. Importantly, no drug interaction between cyclosporine A and tacrolimus, and SOF or DAC has been reported. A recently published multicenter study reported the outcome of 40 HCV transplant recipients who were treated with combination therapy of SOF and RBV for 24 weeks. In this study, most treated patients were infected with genotype 1 and had had previous combination of IFN treatments, and 40% of them had cirrhosis. SVR at 12 weeks after the end of therapy was 70%, with reported major side effects being fatigue, diarrhea, and headache [139].

Concerning FCH, the most severe form of HCV recurrence, a case report was recently published in which the patient was effectively treated with the combination of SOF and DAC, without any relevant side effects [140].

Recently, a multicenter study reported the results of the compassionate treatment of patients with fibrosing cholestatic hepatitis or decompensated cirrhosis due to HCV recurrence after LT [141]. Patients were treated with SOF + RBV with or without Peg-IFN.

The results of 104 patients were analyzed; 52 had an early severe recurrence (diagnosed <12 months after LT) and 52 had cirrhosis (diagnosed >12 months after LT). Twelve patients who underwent re-transplantation were excluded from the efficacy analysis. Of the 92 patients assessed, 54 (59%) achieved SVR at 12 weeks after the end of treatment, with a higher rate (73%, 35/48) in patients with early severe recurrence. Overall, severe adverse events were reported in 49% of patients and 13% of patients died. Although the SVR is good in this difficult-to-treat population, these results are still not satisfactory and are already obsolete. The new combination of DAAs will provide better results with less side effects.

The French experience (CUPILT study) reported the safety and efficacy of SOF and DAC for the treatment of 23 patients with histologically confirmed FCH. The diagnosis of FCH was based on biological criteria (total bilirubin >34 μmol/l, GGT >150 UI/ml, AST >70 UI/ml) and virological criteria (HCV-RNA >6 log UI/ml at 4 weeks post-transplantation) in the absence of vascular and biliary complications. SVR12 was 100%, with excellence in safety and no important interactions with CNI [142].

The combination of SOF and SMV ± RBV has been administered to genotype 1-infected patients with histologically proven HCV recurrence. Mean time between LT and AT was 29 months. Eleven percent of patients had fibrosing cholestatic hepatitis and 29% had a METAVIR score of 3 or

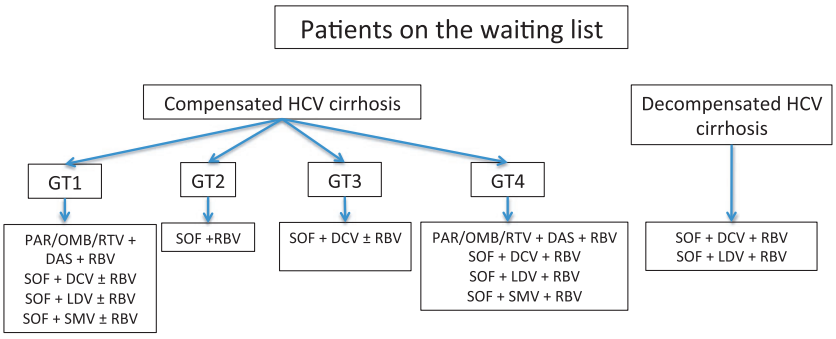

Figure 1 Proposed algorithm for the management of patients with HCV-related liver cirrhosis awaiting liver transplantation.

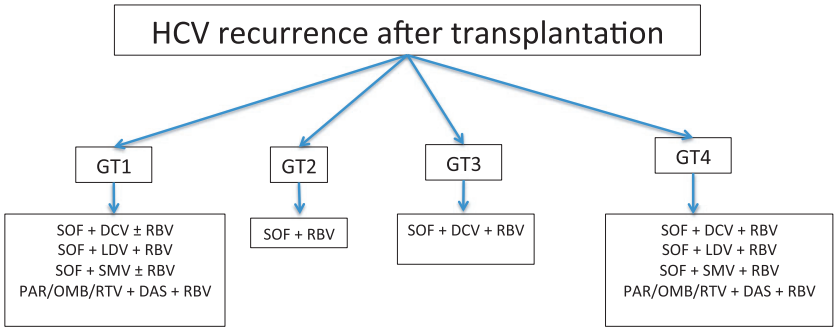

Figure 2 Proposed algorithm for the management of patients with HCV recurrence after liver transplantation.

4. On intention-to-treat analysis, no difference was seen in terms of SVR12 between patients who received RBV (89%) and those who did not (91%). SVR12 was significantly higher in genotype 1a patients with F0–F2 fibrosis stage (97%) compared with F3–F4 fibrosis stage (64%) ($P = 0.01$), while in genotype 1b, no difference was seen between both groups of patients. The treatment was well tolerated and only two patients developed serious side effects: acute pancreatitis in one case, with subsequent reintroduction of therapy, and fatal pulmonary fibrosis in another case [143].

Safety and efficacy of SOF and SMV ± RBV have been also reported in a true life study (TARGET study) in liver transplant recipients. Concerning genotype 1 patients ($n = 131$), SVR4 was 90% ($n = 60/68$), 86% in cirrhotic patients compared with 94% noncirrhotic, and slightly better for genotype 1b (88%) compared with genotype 1a (85%). On multivariate analysis, the predictive factors of a lower probability of SVR4 were the presence of cirrhosis, a previous antiviral treatment, a previous decompensation episode, and the Caucasian race [144].

Another combination has been proposed for patients with HCV recurrence after liver transplantation using SOF + LDV + RBV for 12 or for 24 weeks, with a study reporting a mean time interval between LT and AT of 4.4 years (SOLAR-1 study). In that study, 221 patients were genotype 1 and only 2 patients were genotype 4; most of them were noncirrhotic (F0-F3), treatment-experienced, and non-CC IL-28B. No difference was found according to the therapy duration of 12 weeks versus 24 weeks for F0–F3 patients, CTP A or CTP B. In CTP A patients, SVR was slightly higher compared with CTP B patients: 96% versus 85% (for 12 weeks) and 96% versus 83% (for 24 weeks), respectively. However, the groups were not compared between each other. Overall, the treatment was well tolerated, with few severe side effects [145].

A phase II study (CORAL-1) presented the safety and efficacy of the combination of ABT-450/r/ombitasvir 150 mg/100 mg/25 mg/j + dasabuvir 250 mg × 2/j + RBV administered in patients with fibrosis stage ≤2, naïve of antiviral treatment. A dose reduction was required for the CNI, in particular tacrolimus: 0.5 mg/week or 0.3 mg every three days; CyA 1/5 of the daily dose in one administration. Most of the patients were genotype 1a (85.3%), and the SVR24 was 97.1% ($n = 33/34$). Unfortunately, one patient relapsed at day 3 with the detection of multiple *de novo* mutations: R155K in NS3, M28T + Q30R in NS5A, and G554S in NS5B. Overall, the main side effect was anemia due to RBV. In conclusion, this combination seems promising, but with the downside of RBV use and the interaction with CNI [146]. An algorithm for the management of patients with HCV recurrence after liver transplantation is resumed in Figure 2.

Conclusion

In conclusion, LT recipients with HCV recurrence represent a challenging population, as several factors play a role in HCV disease progression. Compared with the past, the new IFN-free regimens seem to be both effective and safe, even in patients with advanced liver disease, who are typically considered "difficult to treat." Moreover, even if the AUC of SOF is higher in patients with severe renal impairment, recent data show that this drug is well tolerated and safe. Regarding the side effects associated with AT, the possibility of RBV-free regimens seems important to avoid anemia. The absence of CYP3A4 metabolism represents a great advantage in the setting of LT; as a matter of fact, it is associated with a reduction in the incidence of interference with immunosuppressive therapy and consequently of the risk of acute cellular rejection. Moreover, relapse after AT remains an open issue, especially in patients with advanced liver fibrosis/cirrhosis. The best combination of drugs according to genotype has yet to be defined. Furthermore, it would be useful to identify the best strategy to perform mutation-resistance tests in order to choose the more appropriate AT regimen in every patient. Fibroscan can be used to decide which patients warrant immediate start of therapy, but this technique has several limitations and liver biopsy should always be considered, especially in cases in

whom fibrosing cholestatic hepatitis is suspected. The evaluation of the impact of IFN-free antivirals on fibrosis progression is a topic of great interest. In the next future, the HCV burden may strongly be reduced even if the costs of the new drugs could be a critical issue, especially in high-prevalence countries.

Authorship

PB, EDeM and SF: participated in research design, performance of the research and writing of the manuscript, as well as approval of the final manuscript. AZ, MS, FPR and GZ: participated in performance of the research as well as approval of the final manuscript.

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