Chapter 3

Liver Transplantation in Patients with Hepatitis C

Tajana Filipec Kanižaj

Additional information is available at the end of the chapter

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Abstract

As a leading indication for liver transplantation in Western countries, hepatitis C virus (HCV) poses a significant burden both before and after transplantation. Post-transplant disease recurrence occurs in nearly all patients with detectable pre-transplant viremia, therefore compromising the lifesaving significance of transplantation. Many factors involving the donor, recipient and virus have been evaluated throughout the literature, although few have been fully elucidated and implemented in actual clinical practice. Antiviral therapy has been recognized as a cornerstone of HCV infection control; however, experience and success are limited following transplantation in a challenging cohort of patients with liver cirrhosis. Current therapeutic protocols surpass those that were used previously, both in regards to sustained viral response (SVR) and the side-effect profile.

Keywords: hepatitis C, liver transplantation, antiviral treatment, direct-acting drugs, adverse events

1. Introduction

Complications of chronic hepatitis C, mainly decompensated liver cirrhosis and hepatocellular carcinoma (HCC), are leading indications for liver transplantation (LT) in the Western world [1]. Viremic patients at the time of LT have almost a universal recurrence of the disease. The aging of the population with chronic hepatitis C virus (HCV) infection and longer infection duration influence the higher prevalence of advanced liver disease; HCC and the need for LT have doubled over the last decade.

HCV infection significantly impairs patient and allograft survival after liver transplantation. The clinical course of HCV recurrence is highly variable. Compared to the course of HCV disease in patients who underwent transplantation in previous years, with advancement of transplant medicine and the usage of marginal donors and potent immunosuppression,

HCV-related disease progression to cirrhosis is becoming faster and is accompanied by a higher number of complications. Recurrent HCV-related graft failure remains the leading cause of death in these patients. The overall 5-year survival of HCV-positive recipients is slightly lower than that for other indications (60–80%) [2–5].

2. Pathogenesis of disease recurrence

The progression of hepatitis C is accelerated in immunocompromised liver transplant recipients compared with immunocompetent patients both before and after the development of compensated cirrhosis. During reperfusion, the allograft is overwhelmed with HCV that is mainly present in recipient blood and monocytes. The initial decrease of viral titre (linked to the removal of the main viral reservoir) is followed by an exponential increase, reaching pre-transplant levels in a few days [6].

In the first 3 months, most patients (70%) develop acute hepatitis, which is followed by chronic hepatitis (up to 60%) in next 6 months. If untreated, 10–30% of patients develop cirrhosis within 5 years. The majority of other HCV-positive recipients develop graft cirrhosis by 9–12 years post-transplant. In contrast, the median time to cirrhosis in the non-transplanted population is >30 years. The rate of decompensation is >40% at 1 year and >70% at 3 years in LT recipients versus <5 and <10%, respectively, in immunocompetent patients [7].

The variables leading to different patterns of disease recurrence in individual patients are not well understood. Up to 50% of recipients develop mild to moderate inflammation on liver biopsy; 20% results in minimal changes and 20–40% leads to progressive inflammatory changes with high-grade histological damages [8]. Due to the direct effects of the virus on liver cells, up to 15% of graft recipients develop the most detrimental pattern of disease recurrence with unfavorable prognosis—fibrosing cholestatic hepatitis (FCH). The development of FCH may be more common in patients with higher HCV viral titre and higher levels of immunosuppressive medications, usually due to treatment of acute cellular rejection [9]. If untreated, FCH rapidly proceeds to liver failure.

Several variables, including donor characteristics (donor age and type), recipient characteristics (female gender, HIV co-infection), viral characteristics (genotype (G) 1b, higher viral titre and IL28B non-CC polymorphism), a higher degree and type of immunosuppression, earlier timing of recurrence and early severe histological findings are implicated in the outcome of hepatitis C patients post-transplantation [10]. None of previously mentioned factors have been extensively validated, achieved universal consensus among the literature or permitted clinically important intervention.

2.1. The role of immunosuppression

There is much interest in the influence, level and type of immunosuppression following LT on the severity of disease recurrence. The impact is most pronounced when high-intensity regimens are used to treat acute rejection, particularly with high-dose steroid boluses and anti-lymphocyte antibody preparations [11–13]. There are no convincing data to support the

use of any specific induction or maintenance regimen, and it is likely that the choice of initial calcineurin inhibitor (tacrolimus or cyclosporine) does not significantly impact overall outcomes in HCV-positive liver transplant recipients [14].

3. Diagnosis of HCV recurrence post-transplant

The initial drop in transaminase level during the early post-transplant setting is usually followed by only minimally to mildly elevated alanine aminotransferase (ALT) levels in later post-transplant periods. Further increases of liver enzymes are influenced not only by the degree of HCV recurrence but also the wide spectrum of other post-transplant complications such as acute cellular rejection, reperfusion or drug-induced liver injury, vascular and biliary complications.

Consequently, the diagnosis of graft HCV infection is based on the combined analysis of polymerase chain reaction (PCR) and liver biopsy findings. Liver biopsy remains the gold standard in the detection of the severity of disease progression and the differentiation of liver pathology (the exclusion of other diseases). Except in the setting of FCH liver biopsy, findings are mostly mild and nonspecific. They include periportal inflammation, lobular hepatocytes ballooning, acidophilic bodies or lobular apoptosis. Some of these features are also seen in acute cellular rejection. High blood levels of cholestatic enzymes are characteristic of FCH, including extensive dense portal fibrosis immature fibrous bands extending into the sinusoidal spaces, ductular proliferation, cholestasis and moderate mononuclear inflammation on liver graft biopsies. Differentiating rejection from hepatitis C based only on pathology can be difficult, in real clinical practice, final clinical judgment is reconsidering also the timing after transplantation and clinical features (e.g., the degree of baseline immunosuppression and prior rejection episodes) [15]. Substantial periportal sinusoidal fibrosis in early biopsies (<6 months) has been shown to be a good predictor of severe HCV recurrence.

Even in situations of typical HCV recurrence, final clinical judgment is performed after the exclusion of other possible causes of post-transplant liver injury (usually based on the combination of clinical examination, various laboratory tests, liver ultrasound and liver biopsy findings).

Methods of non-invasive fibrosis measurement were investigated in HCV recurrence after LT. In a systematic review that pooled five studies of patients with recurrent HCV, the sensitivity and specificity for ultrasound-based elastography for predicting significant fibrosis were both 83%, and its sensitivity and specificity for predicting cirrhosis were 98 and 84%, respectively [16].

4. Approaches to the treatment of HCV recurrence following liver transplantation

Along with the impact of the previously mentioned factors on disease recurrence and overall patient and graft survival, antiviral therapy success rates appear to be one of the most important factors.

Several strategies for HCV treatment in the setting of LT have been attempted: treatment prior to LT, immediate or perioperative prophylaxis of HCV graft infection, early pre-emptive HCV therapy and treatment of established recurrent graft disease.

There is an open debate regarding which of the previously stated options are preferable following liver transplantation. Thus far, a consensus has not been reached because these four approaches have not been prospectively compared in appropriately powered randomized trials using clinical endpoints. Unfortunately, due to the heterogeneity of end-stage liver disease, the small number of patients, and the highly complex treatment of liver transplant candidates and recipients, it is unlikely that such trials will be performed in a randomized controlled fashion. In their absence, the recommendations are guided by the results of clinical trials that assess each approach separately as well as data from the real-world and the panel members' experiences.

4.1. Treatment prior to LT

Strategies to eradicate HCV infection before LT is directed at preventing disease recurrence, leading to significant improvement in liver function and prolongation or avoidance of the need for LT (delisting of selected patients). Interferon (IFN)-based regimens are contraindicated in decompensated patients due to the high rate of side effects (mainly infections and further liver disease deterioration). In the IFN era, less than 25% of LT candidates were eligible for treatment. The accomplished eradication rate (sustained viral response, SVR) was 8–30%. The main reason for the generally lower SVR rates in patients with liver cirrhosis was poor treatment tolerability with substantially high rates of serious adverse events (SAE), leading to dose reductions (70%) and therapy discontinuation (30%). With the availability of new generations of direct-acting agents (DAA) with an improved safety profile, more LT candidates are eligible for treatment. SVR rates greater than 95% can now be reached in patients with compensated cirrhosis who are undergoing transplantation for coexistent HCC. Although very good, slightly lower SVR rates (approximately 80%) are expected with the use of currently available DAA in case of decompensated cirrhosis (**Figure 1**) [17–21].

Regarding this treatment approach, there are many open questions. While deciding to treat liver transplant candidates on the waiting list, we must keep in mind that the time of LT and the duration of antiviral therapy cannot be predicted. Consequently, some of the patients may be transplanted before the virus has been cleared. In addition, there remain uncertainties regarding the safety of DAA therapy and the outcomes among those with advanced liver insufficiency. Is there indeed a point after which antiviral therapy is futile? It is unknown whether meaningful functional hepatic recovery is possible in most eradicated HCV patients with advanced cirrhosis, how long such recovery would take, whether short-term positive effects on Model of End-Stage Liver Disease (MELD) will indeed translate into long-term clinical benefits with a reduced occurrence of HCC, decompensation or all-cause mortality following DAA therapy. Most of the patients will keep a diseased liver with the risk of subsequent decompensations, HCC occurrence and death and thus could lose an opportunity to cure both the liver disease and the infection with LT (MELD purgatory). So far, it is yet to be explored whether DAA therapy can reduce the risk of subsequent decompensations, HCC occurrence and death, or, even in patients with previous HCC or increased risk of HCC occurrence.

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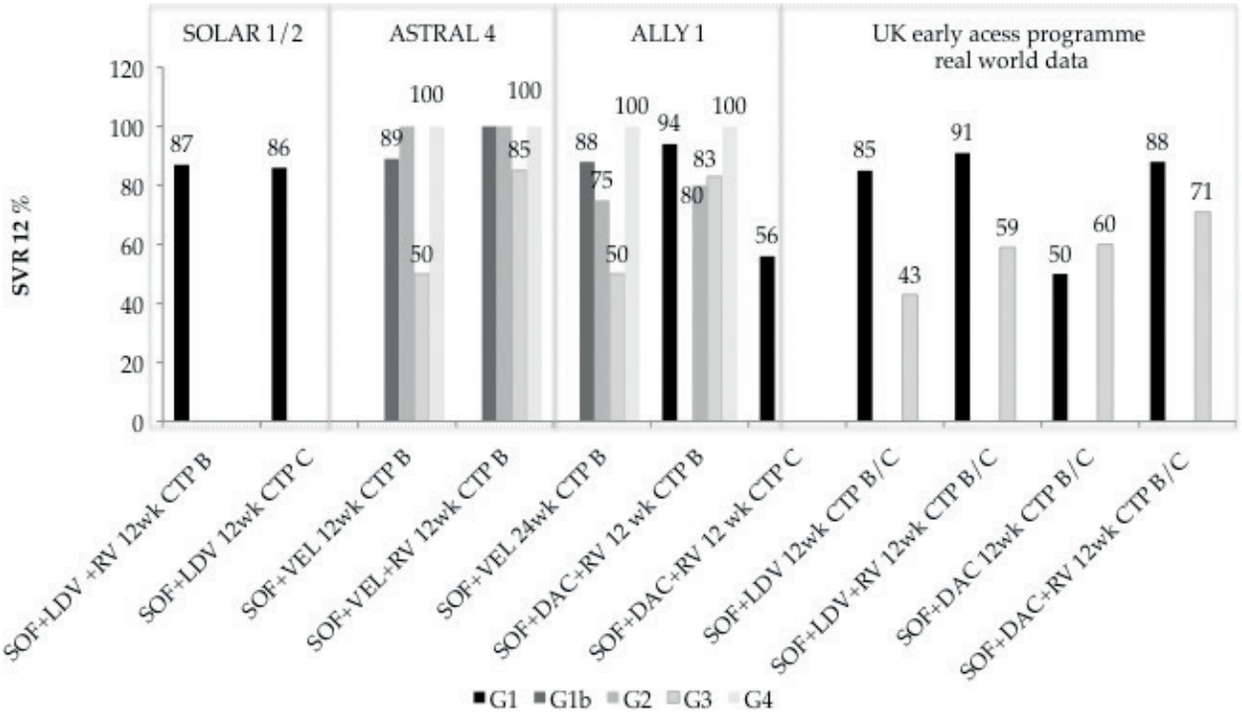

Figure 1. Twelve week sustained viral response (SVR12) in patients with decompensated cirrhosis (adapted from Refs. [18–22]).

Due to a favorable side-effect profile, treatment of decompensated patients with new DAA drugs such as sofosbuvir (SOF), ledipasvir (LDV), velpatasvir (VEL) or daclatasvir (DAC)-based regimens, is recommended (**Table 1**). Recently, many new data from clinical studies are emerging with more potent DAA combinations.

4.1.1. Clinical study data on DAA treatment in LT candidates

The proof of concept of DAA treatment for LT candidates came from a phase 2, open-label study on 61 patients with (all genotypes) HCV liver cirrhosis (Child-Turcotte-Pugh score, CTP ≤ 7; Model of End-Stage Liver Disease, MELD < 22) who were on waiting lists for liver transplantation. Patients received up to 48 weeks of SOF + RV. Among 46 patients who underwent LT, 43 had negative viremia at the time of LT and 70% remained negative 12 weeks after LT. Overall, 63% of transplanted patients had a virological response at 12 weeks post-transplant. Recurrence was inversely related to the number of days of undetectable HCV viremia prior to LT. None of the patients who were negative for more than 4 weeks before LT experienced HCV recurrence [17]. However, with the development of new drugs, this combination is suboptimal and is, thus, not recommended.

The SOLAR I study assessed treatment with the SOF + LDV + RV for 12–24 weeks in patients infected with HCV genotypes 1 (99%) or 4 (1%). Patients were stratified to two cohorts depending on the time of treatment: cohort A (decompensated cirrhosis and CTP B/C) treated before LT or cohort B treated after LT. Patients in cohort A achieved SVR12 rates of 87–89% in CTP B patients and 86–87% in CTP C patients, respectively, after treatment for 12–24 weeks [17]. The SOLAR II study had an identical design. Data revealed SVR12 rates of 87–96% in CTP

Genotype	Compensated cirrhosis regimen*	Decompensated cirrhosis (CTP B/C) regimen*
G1	SOF + LDV 12 wk; G1a experienced 24 wk or + RV 12 wk	SOF + LDV + RV 12 wk
	3D G1b 12 wk, G1a + RV 24 wk	SOF + DAC + RV 12 wk
	SOF + DAC 12 wk; G1a experienced 24 wk or + RV 12 wk	SOF + VEL + RV 12 wk
	SOF + VEL 12 wk	
	GRA + ELB G1b 12 wk; G1a 12 wk if HCV RNA ≤800,000 (5.9 log) IU/ml or + RV 16 wk HCV RNA >800,000 (5.9 log) IU/ml	
G2	SOF + VEL 12 wk	SOF + DAC + RV 12 wk
	SOF + DAC 12 wk	SOF + VEL + RV 12 wk
G3	SOF + DAC + RV 24 wk	SOF + DAC + RV 24 wk
	SOF + VEL 24 wk, + RV 12 wk	SOF + VEL + RV 24 wk
G4	SOF + LDV 12 wk; experienced 24 wk or + RV 12 wk	SOF + LDV + RV 12 wk
	2D + RV 12 wk	SOF + DAC + RV 12 wk
	SOF + DAC 12 wk, experienced 24 wk or + RV 12 wk	SOF + VEL + RV 12 wk
	SOF + VEL 12 wk	
	GRA + ELB 12 wk, experienced 12 wk if HCV RNA ≤800,000 (5.9 log) IU/ml or + RV 16 wk HCV RNA >800,000 (5.9 log) IU/ml	
	SOF + SIM 12 wk, experienced 24 wk or + RV 12 wk	
G5,6	SOF + LDV 12 wk, experienced 24 wk or + RV 12 wk	SOF + LDV + RV 12 wk
	SOF + DAC 12 wk, experienced 24 wk or + RV 12 wk	SOF + DAC + RV 12 wk
	SOF + VEL 12 wk	SOF + VEL + RV 12 wk

SOF, sofosbuvir (400 mg/day); LDV, ledipasvir (90 mg/day); DAC, daclatasvir (60 mg/day); 3D, ombitasvir (25 mg/day)/paritaprevir (150 mg/day)/ritonavir (100 mg/day) + dasabuvir (250 mg twice daily); 2D, ombitasvir (25 mg/day)/paritaprevir (150 mg/day)/ritonavir (100 mg/day); VEL, velpatasvir (100 mg/day); GRA, grazeoprevir (100 mg/day); ELB, elbasvir (50 mg/day); RV, ribavirin (when ribavirin is used, especially in patients with advanced recurrent disease, it may need be started at a dose of 600 mg daily, with subsequent increase in the dose as tolerated until reaching a dose of 1000 mg daily (for patients <75 kg) or 1200 mg daily (for patients ≥ 75 kg). The dosing of ribavirin should take into account the patient's creatinine clearance and hemoglobin level); wk, weeks; CTP, Child-Turcotte-Pugh score.

*If no RV eligible 24 weeks.

Table 1. Recommended HCV treatment options for liver transplant candidates and patients with liver cirrhosis (adapted from Ref. [26]).

B patients and 85–88% in CTP C patients, respectively, after treatment for 12–24 weeks. The MELD and CTP scores improved in approximately half of the treated patients. Up to 88% of patients with baseline CTP B/C scores exhibited improved CTP scores (35% CTP B to A, 48% CTP C to B, but only 5% CTP C to A) [19]. About 4% of patients with CTP score A deteriorated to CTP B; 95% experienced adverse events (AE); 14–28% experienced SAE, but only 1–5% of SAE were related to DAA. No deaths were proven to be treatment related.

The ASTRAL 4 study evaluated the efficacy, safety and tolerability of SOF + velpatasvir (VEL) ± RV for 12 weeks and SOF/VEL for 24 weeks in genotype 1–6 patients with CTP B cirrhosis. The overall SVR12 rates were 83% among patients who received 12 weeks of SOF + VEL, 94%

among those who received 12 weeks of SOF + VEL + RV, and 86% among those who received 24 weeks of SOF + VEL. Post hoc analysis did not detect any significant differences in the rates of SVR among the three study groups. Among genotype three patients, 85% achieved SVR12 with the SOF + VEL + RV 12-week treatment. SAE occurred in 19% of the patients who received SOF + VEL for 12 weeks, 16% of the patients who received SOF + VEL + RV for 12 weeks, and 18% of the patients who received SOF + VEL for 24 weeks. The most common AE were fatigue (29%), nausea (23%), headache (22%) and anemia (31%) in the patients receiving RV. A total of 51% of patients with a baseline MELD score <15 exhibited improved MELD scores at week 12 post-treatment and 27% of patients exhibited worsened MELD scores. A total of 81% of the patients with a baseline MELD score ≥15 exhibited improved MELD scores, and 7% of patients exhibited worsened MELD scores [20].

In a multicentre, prospective, open-label, phase-3 study (ALLY I), a combination therapy of DAC + SOF + RV for 12 weeks was evaluated in 60 (genotypes 1–6) patients with advanced cirrhosis (80% CTP B/C) or post-liver transplant HCV recurrence. In patients with advanced cirrhosis, the overall SVR12 rate was 94% (92% for CTP A, 94% CTP B and 56% CTP C). The overall SVR12 rate in genotype (G) 1 was 82% (76% G1a and 100% G1b), and based on the baseline cirrhosis stage, the overall SVR12 rate was 91% for CTP A, 92% for CTP B and 50% for CTP C patients. The corresponding SVR12 rates in patients with genotypes 2, 3 and 4 were 80, 83 and 100%, respectively. SAE occurred in 17% of patients. There were no treatment-related SAE and no deaths due to treatment. The overall CTP scores improved in 60% of patients and worsened in 15% of patients. Among patients with baseline CTP B and C scores, 50% improved to class A and B, respectively. MELD scores improved in 47% of patients and worsened in 35% of patients [21].

Experience from the United Kingdom Expanded Access Programme in real-world patients with advanced stages of liver cirrhosis (CTP B/C) who were treated with SOF + DAC or LDV ± RV for 12 weeks revealed an overall SVR12 rate of 82%. The SVR12 rates for G1 patients were 85% for SOF + LDV, 91% for SOF + LVD + RV, 50% for SOF + DAC and 88% for the SOF + DAC + RV regimen. In patients with decompensated cirrhosis infected with genotype 3, the SVR12 rates were 60% for SOF + DAC and 71% SOF + DAC + RV 12-week regimens. Viral clearance was associated with improvement in liver function within 6 months compared to untreated patients. Patients with initial serum albumin levels <35 g/L, aged >65 or with low (<135 mmol/L) baseline serum sodium concentrations were least likely to benefit from therapy [22]. When compared to the outcome in first 6 months from the start of treatment and to untreated patients, after 6 months of treatment, there was a reduction in the incidence of decompensation (7% in months 6–15 versus 18% in months 0–6 for treated patients and 28% in untreated patients) and in the incidence of MELD score worsening by >2 points (23% in months 0–6 for treated patients versus 38% in untreated patients). There was no significant difference in HCC incidence (2.5% in months 6–15 versus 4% in months 0–6 for treated patients and 4% in untreated patients). The long-term impact of HCV treatment in patients with decompensated cirrhosis remains to be determined since in longer follow-up studies (15 months), AE-free survival among treated patients with CTP C or a MELD score >14 at baseline remained poor [23].

Data about the possibility of delisting patients with improved liver function from the LT list are scarce. In a multicentre, European, retrospective real-world study on 103 LT candidates in 11 transplant centers, DAA-based therapy reversed liver dysfunction in approximately one patient out of three patients who were put on hold, and enabled delisting in approximately 1 patient out of 5 in 60 weeks. Patients with lower MELD scores (<16) had higher chances of being delisted. The short-term benefits observed must be balanced with the respective risks of LT and of not undergoing LT. The long-term clinical benefit of therapy was not assessed [24].

According to all of the presented data, the severity of liver disease at the time of antiviral treatment initiation seems to be a more relevant determinant of early mortality than the virological response and should thus be considered to guide patient prioritization for LT. According to European guidelines, patients with decompensated cirrhosis and an indication for LT with a MELD score ≥18–20 should be transplanted first and then treated after transplantation [25, 26].

4.2. Perioperative treatment

There is limited data about the benefits of perioperative treatment of HCV-positive recipients. In a small study on 16 patients treated with LED + SOF for 4 weeks (starting at day of LT), an SVR12 rate of 88% was achieved [27].

4.3. Early pre-emptive HCV therapy

The use of DAA combinations in this setting has not yet been studied, and many centers now treat recurrent HCV with the regimens detailed below during the early post-operative period once the patient is stable. Studies regarding the safety and optimal timing of treatment in this setting are needed [26]. Meta-analyses of the IFN-based studies did not identify benefits for patients who received early pre-emptive antiviral therapy following LT and those who did not [28].

4.4. Treatment of post-transplant HCV disease recurrence

In the post-liver transplant setting, IFN-based therapies could be used, but they induced numerous and often severe side effects; additionally, their results were disappointing (SVR12 30–40%). The latest European guidelines recommend DAA as the most suitable in the post-transplant setting, including combinations of SOF with LDV, VEL and DAC with or without RV (**Table 2**) [26]. All patients should be considered for therapy. Treatment should be initiated early after LT, ideally as early as possible when the patient is stabilized (generally after the first 3 months) because the SVR12 rates decrease in patients with advanced post-transplant liver disease. Patients with FCH, the presence of moderate to extensive fibrosis or portal hypertension 1 year after LT are associated with rapid disease progression and graft loss and require more urgent antiviral treatment [26]. An SVR12 rate higher than 95% can be accomplished with new DAA drugs in LT recipients (**Figure 2**). Due to possible drug-to-drug interactions and post-transplant complications, therapy should be performed only at centers with considerable experience in managing transplanted patients.

Genotype	Regimen*
G1	SOF + LDV + RV 12 wk
	SOF + DAC + RV 12 wk
	SOF + VEL + RV 12 wk (24 wk CTP B/C)
G2	SOF + DAC + RV 12 wk
	SOF + VEL + RV for 12 weeks (24 wk CTP B/C)
G3	SOF + DAC + RV 24 wk
	SOF + VEL + RV 24 wk
G4	SOF + LDV + RV 12 wk
	SOF + DAC + RV 12 wk
	SOF + VEL + RV 12 wk (24 wk CTP B/C)
G5,6	SOF + LDV + RV 12 wk
	SOF + DAC + RV 12 wk
	SOF + VEL + RV 12 wk (24 wk CTP B/C)

SOF, sofosbuvir (400 mg/day); LDV, ledipasvir (90 mg/day); DAC, daclatasvir (60 mg/day); VEL, velpatasvir (100 mg/day); RV, ribavirin (when RV is used, especially in patients with advanced recurrent disease, it may need be started at a dose of 600 mg daily, with subsequent increase in the dose as tolerated until reaching a dose of 1000 mg daily (for patients <75 kg) or 1200 mg daily (for patients ≥ 75 kg). The dosing of RV should take into account the patient's creatinine clearance and hemoglobin level); wk, weeks; CTP, Child-Turcotte-Pugh score.

*If no RV eligible 24 weeks.

Table 2. Recommended treatment options for patients with transplanted liver and HCV infection (adapted from Ref. [26]).

4.4.1. Clinical study data on DAA treatment of transplanted patients

Fixed combination therapy of SOF + LDV + RV for 12–24 weeks has been studied (SOLAR I and II) in transplanted patients with genotypes 1 and 4 and a wide range of liver disease stages (METAVIR fibrosis stage 1–3 (F0–3) and CTP A-C). In the 12- and 24-week treatment groups, SVR12 rates of 96 and 98% were achieved in patients with baseline F0–3. In both treatment duration groups, the SVR12 rate was 96% for CTP A patients. The efficacy was lower in patients with CTP B cirrhosis (85 and 88% SVR12) or CTP C cirrhosis (60 and 75% SVR12) in the 12- and 24-week groups, respectively [18]. Similar results were obtained in the SOLAR II study. SVR12 was achieved in 98 and 100% of patients with F0–3, in 100 and 96% of patients with CTP A, in 95 and 100% of patients with CTP B and in 50 and 80% of patients with C cirrhosis with 12 and 24 weeks of treatment, respectively. SVR among patients with FCH was 100% [19]. In both studies, unsatisfactory viral eradication was observed for patients with CTP C liver cirrhosis. This could be explained by the small number of patients within the CTP C groups in both studies, consequently additional data are needed for final conclusions. In summary, 95% of patients experienced AE, and 15–28% of patients experienced SAE depending on the severity of the liver disease (F0–3/CTP A: 15% and CTP B/C: 28%). Up to 5% of patients discontinued the study due to SAE [18, 19].

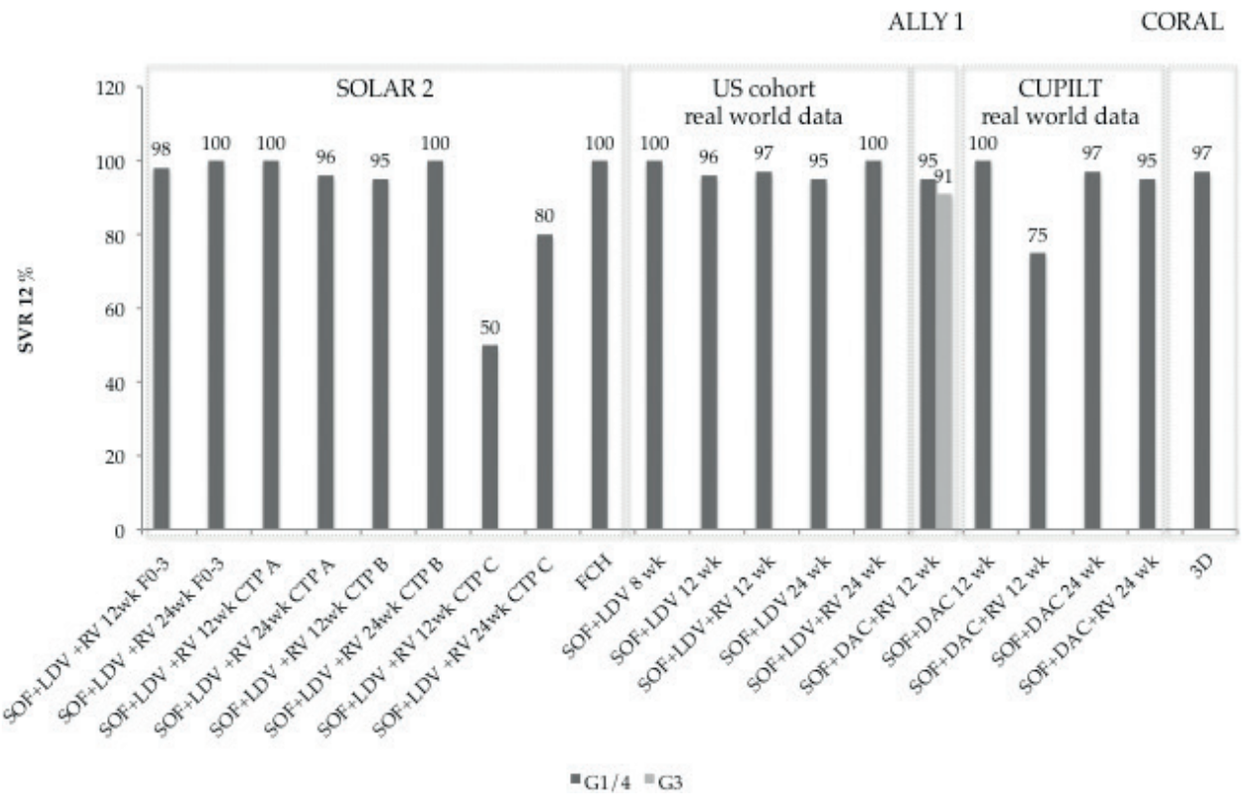

Figure 2. Twelve week sustained viral response (SVR12) in patients with pos-transplantation HCV recurrence (adapted from Ref. [19, 21, 29–31]).

The same conclusions were revealed in real-world studies. In a large retrospective US cohort study, 204 patients (21% advanced fibrosis, 49% treatment-experienced and 66% genotype 1) were treated with SOF + LDV ± RV for 8, 12 or 24 weeks. The overall SVR12 rate was 96% (100% for 8 weeks of SOF + LDV, 96% for 12 weeks of SOF + LDV, 97% for 12 weeks of SOF + LDV + RV, 95% for 24 weeks of SOF + LDV and 100% for 24 weeks of SOF + LDV + RV) [29]. Excellent results in groups without RV treatment raise the question of its universal need in all transplanted patients. Since all controlled studies have been done using RV-based regimens, prospective studies are required for a final conclusion.

In a phase-3 ALLY I study, a combination of SOF + DAC + RV was administered to 53 transplanted patients (77% genotype 1); 95 and 91% patients with genotypes 1 and 3 infection achieved SVR12, respectively. Overall, 99% of patients experienced AE, 9% of patients experienced SAE and 2% of patients discontinued the drug therapy due to drug-related AE [21].

Real-world data from the CUPILT study revealed similar results. A total of 137 transplanted patients (81% genotype 1 and 31% cirrhosis) were treated with SOF + DAC ± RV for 12 weeks. Overall the SVR12 rate was 96% under the intention-to-treat analysis, and it was 99% when non-virological failures were excluded (75% for 12 weeks of SOF + DAC + RV, 100% for 12 weeks of SOF + DAC, 95% for 24 weeks of SOF + DAC + RV and 97% for 24 weeks of SOF + DAC). The rate of SAE reached 17.5% with 3% of patients discontinuing treatment prematurely because of SAE. A slight but significant reduction in creatinine clearance was reported. No clinically relevant drug-drug interactions were noted, although 52% of patients required a change in the dosage of immunosuppressive drugs [30].

A trial with SOF + VEL combination therapy is ongoing for transplanted patients.

In a study of 34 patients with HCV G1 recurrence following liver transplantation and METAVIR stage F0–F2 fibrosis, patients were given ombitasvir/ritonavir-boosted paritaprevir + dasabuvir + RV (3D therapy). Patients were treated for 24 weeks. An SVR at 12 and 24 weeks post-treatment was achieved by 97% of patients. Overall, 97% of patients experienced adverse events with only 6% of patients experiencing serious adverse events. Common adverse events included fatigue, headache and cough. One patient (3%) discontinued the study drugs due to adverse events. There were no episodes of graft rejection [31]. The 3D treatment required dosing modifications for calcineurin inhibitors tacrolimus and ciclosporin. The recommended dose of tacrolimus should be reduced to 0.5 mg per week or 0.2 mg every 3 days, and cyclosporine should be reduced to one-fifth of the daily pre-3D therapy dose and given once a day with regular immunosuppressive drug level monitoring. This combination should not be administered with everolimus. SOF, LDV and DAC do not seem to interact with calcineurin inhibitors. However, close monitoring before, during and after DAA therapy is essential. In the CUPILT study, 59% of the patients treated with SOF and DAC after LT had to change the dose of one immunosuppressive drug during therapy.

Even in patients with decompensated graft cirrhosis, treatment with DAA could improvement MELD and CTP scores. In the SOLAR II study, 28% of baseline CTP B patients reversed to CTP A and 68% of the CTP C patients reversed to CTP B [19]. In the ALLY I study, these percentages were 50 and 46%, respectively [21].

The optimum timing for the initiation of therapy post-transplantation remains to be determined. Based on the tolerability of the classic IFN-based regimen, the most common initial approach was to treat graft hepatitis after histological damage was confirmed (fibrosis stage 2 or higher on the METAVIR score or severe and rapid progression of fibrosis as observed in FCH) and before clinical decompensation had developed. With the DAAs, there are no limitations on treating post-transplant recurrence early after LT, including patients with decompensated cirrhosis or those with fibrosing cholestatic hepatitis (FCH)—a life-threatening form of HCV recurrence. This strategy is even more reasonable when considering that treatment in patients with decompensated graft cirrhosis is related to reduced SVR12 rates [32].

5. Conclusions

HCV-associated cirrhosis is the most common indication for LT in the Western world. Recurrent HCV infection still remains a major cause of morbidity and mortality post-transplantation. The clinical course of HCV infection appears to be accelerated compared with the pre-transplant setting, and several patterns of recurrence have been described. Many predictors of outcome following LT have been described, but their accuracy in predicting the course of recurrence in individual patients or in guiding interventions is uncertain. With the evolution of new antiviral drugs and more precise and clear knowledge of HCV disease recurrence, promising results have begun to emerge in the complex field of liver LT. Treatment regimens based on DAAs are highly effective and well tolerated in both pre- and post-transplant patients, including patients with decompensated cirrhosis or those with FCH. All patients who do not achieve an SVR pre-transplant should be treated post-transplant. The optimal

timing is uncertain, and the decision of when to treat must be made on an individual basis. SVR rates greater than 95% could be achieved. From a safety point of view, very few severe adverse events have been reported among studies. Therapy should only be attempted at centers with considerable experience in managing post-transplantation patients.

Author details

Tajana Filipec Kanižaj

Address all correspondence to: tajana.filipec@gmail.com

Department of Gastroenterology, University Hospital Merkur, School of Medicine, University of Zagreb, Zagreb, Croatia

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