Chapter

Liver Transplantation and HCV Genotype 4

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Abstract

End-stage liver disease secondary to hepatitis C virus (HCV) infection is a major indication for liver transplantation (LT) worldwide. Previous studies have shown a negative impact of HCV on patient and graft survival leading to an inferior transplant outcome when compared to other liver transplant indications. The percentage of HCV patients infected with genotype 4 (G4) among recipients of OLT varies depending on geographic location. In the Middle East HCV-G4 infection is the most common genotype among transplant recipients. Direct antiviral agents (DAAs) have revolutionized the management of HCV infection in the pre- and post-transplant setting. Recent clinical trials have shown high sustained virologic response rates, shorter durations of treatment, and decreased adverse events when compared with the previous treatment of pegylated interferon (PEG-IFN)-based therapy. However, most of these studies were performed in HCV-G1-infected patients. Due to the low prevalence of HCV-G4 in Europe and the USA, this genotype has not been adequately studied in prospective trials evaluating treatment outcomes. The aim of this chapter is to summarize the natural history and treatment outcome of HCV-G4 in the liver transplant setting, with particular attention to new HCV therapies.

Keywords: cirrhosis, direct antiviral agents, genotype 4, hepatitis C, liver transplantation

1. Introduction

Hepatitis C virus (HCV) infection is one of the main indications for liver transplantation (LT) and is a major cause of liver related mortality [1, 2]. Patients transplanted for HCV-related cirrhosis have a worse 5-year survival than those with other indications [3, 4]. HCV eradication prior to LT will likely improve the outcome by eliminating the risk of post-transplant recurrence. Over the last decade, the development of highly effectively DAA agents has allowed for the safe and successful treatment of HCV, shrinking the number of recipients with chronic HCV and improving the post-transplant outcome [5].

Hepatitis C genotype 4 (HCV-G4) is the most prevalent genotype in the Middle East, and Northern Africa [6–9]. Egypt is the most affected nation by HCV and HCV-G4 accounted for 94. 1% of infections. More than 90% of liver transplants in Egypt are for HCV –G4 [10]. Earlier studies from Saudi Arabia also demonstrated that HCV-G4 is the leading indication for liver transplantation [11]. On the other hand, HCV-G4 is a rare indication for liver transplantation in other parts of the world [12, 13].

The frequency of infection with HCV-G4 is also increasing in European countries, particularly among intravenous drug users and immigrants [14–17]. HCV-G4 has not been adequately studied in prospective trials evaluating treatment outcomes and remains the least studied variant. However, over the past five years' data on treatment outcomes of HCV-G4 in the DAA era has been accumulating.

The treatment outcome of HCV-G4 in the interferon era has been reported in multiple studies [18–23]. A higher rate of spontaneous resolution after acute HCV-G4 infection has been reported [24, 25]. Other studies associated HCV-G4 infection with hepatic steatosis [26, 27]. These observations may have an impact on the natural history and treatment outcomes of HCV-G4.

Direct antiviral agents (DAAs) represent a breakthrough in the management of HCV. First generation DAAs (telaprevir, boceprevir) in post-liver transplant patients resulted in sustained virological response of up to 60% with telaprevir in HCV-G1. However, significant side effects including severe anemia, skin complications and significant drug interactions resulted in major concerns [28]. These agents are currently contraindicated and are not used anymore. Second line direct-acting antiviral DAAs have emerged with better safety and efficacy profiles, leading to dramatic changes in the practice of HCV management [29–36]. An international, multicenter, long-term follow-up study of 530 patients with chronic HCV infection who received interferon based therapy demonstrated that among patients with advanced hepatic fibrosis, sustained virological response was associated with lower all-cause mortality [37]. The revolutionary discovery of DAAs makes chronic HCV infection a curable disease in patients with advanced liver disease. Liver function may improve after antiviral therapy in patients on the waiting list and could result in patient delisting. Following liver transplantation, DAA treatment is also highly effective so that postponing antiviral treatment to the post-transplant setting may be of benefit for certain patients. The, aim of this Chapter is to examine the natural history and treatment outcomes of HCV-G4 following liver transplantation. This review includes all published studies and abstracts involving HCV-G4 patients.

2. Natural history of HCV-G4 after liver transplantation

The introduction of DAAs is a significant therapeutic breakthrough in the management of HCV infection. With a very high cure rate, a large proportion of LT candidates and recipients can be cured of HCV infection by DAA therapies that are safe and well-tolerated. Due to the high efficacy of these drugs, a major decline was observed in the number of LT performed both in patients with decompensated cirrhosis with HCV and in those with hepatocellular carcinoma associated with HCV worldwide [38–40]. Furthermore, the survival of LT recipients with HCV-related liver disease has clearly improved because of treatment for HCV recurrence. The advent of efficacious DAA therapy to treat HCV recurrence, resulted in an increasing trend to use HCV seropositive donors for both HCV seropositive and seronegative recipients with excellent outcome [41].

Re-infection of the graft is universal after liver transplantation regardless of genotype and has a negative impact on medium and long-term outcomes [42]. Western studies evaluating the natural history of HCV- G4 in the pre DAA era suggested a worse outcome compared to other genotypes. Zekry et al. analyzed factors that predicted outcome of HCV-liver transplant recipients in the Australian and New Zealand communities. Among 182 patient transplanted for HCV including 16 patients infected with HCV-G4 and a median follow-up of 4 years. HCV-G4 was associated with an increased risk of re-transplantation and death in univariate and multivariate analyses [43]. Whether this difference in outcomes was related to the

pathogenicity of HCV-G4 or to other factors not examined in this study, including donor age, immunosuppression, and compliance with medications, is not clear (**Table 1**). Furthermore, patients infected with HCV-G4 in this study were older and more likely to have coexisting hepatocellular carcinoma. In a larger study Gane *et al*. investigated the impact of persistent HCV infection after liver transplantation on patient and graft survival and the effects of the HCV genotype on the severity of recurrent hepatitis. 149 patients with HCV including 14 patients with HCV-G4 infection were followed for a median of 36 months; 623 patients without HCV infection who underwent liver transplantation for end-stage chronic liver disease were used as a control group. Approximately 50% of HCV-G4 had progressive liver disease (moderate hepatitis or cirrhosis) during the follow-up period [44]. In the same study, patients infected with G1b had the worst outcome, whereas patients infected with G2 and G3 had less severe disease recurrence. A more detailed single center study from the UK aimed at studying the impact of HCV-G4 on transplant outcome. The study group included 128 patients who underwent transplantation for HCV infection: 28 patients, genotype 1; 11 patients, genotype 2; 19 patients, genotype 3; and 32 Middle Eastern patients with genotype 4 [45]. A significantly higher fibrosis progression rate was observed in HCV-G4 patients compared with non-G4 patients, although their rates of survival were similar. The five-year cumulative rates for the development of cirrhosis or severe fibrosis were 84% in HCV-G4-infected patients and 24% in patients infected with other genotypes. In the United Kingdom, those Middle Eastern patients maybe the recipients of donated organs only when available organs are declined by all UK transplant centers for UK-born patients. Thus, genotype-4 patients are more likely to receive marginal livers or livers from an older donor. This policy may have led to the selection of inferior grafts for the HCV-G4 patients, who were predominantly non-UK citizens, leading to inferior results in these patients. It has been clearly shown that advanced donor age has a negative impact on the transplant outcome including rapid progression to fibrosis and cirrhosis [46–48].

On the other hand, studies from the Middle East show a more favorable outcome. According to reports from Saudi Arabia and Egypt, overall graft and patient survival for HCV-G4 are comparable to rates reported in the international literature. Reports from Saudi Arabia reveal an overall three-year graft and patient survival rates of 90% and 80%, respectively [11, 49–53]. Similarly, in Egypt, where many

Factors affecting transplant outcome
Viral load
Genotype
Coinfections
Alcohol consumption
Compliance
Chronic kidney disease
Sarcopenia
Steatosis
Donor Age
Immunosuppression
Rejection

Table 1.
Factors affecting the outcome of HCV-related transplantation

active living–related liver transplant programs exist and HCV-G4 represents more than 90% of cases, graft and patient survival rates are approximately 86% [10].

Multiple recent studies from the Middle east evaluated the natural history of HCV-G4 following liver transplantation. A study from Saudi Arabia reported the results of patients who had biopsy-proven recurrent hepatitis C infection and made a comparison between patients with HCV-4 and non-HCV-4 genotype. They clearly demonstrated no significant differences between these two groups in terms of clinical, epidemiological, and histological factors and outcome. They found that in the initial liver biopsy, which was performed after a mean time from transplantation of more than 2 years, there were only four patients who had fibrosis scores greater than stage 3. Two of these patients progressed to cirrhosis on subsequent biopsies [54]. Among many factors included in that analysis, the only factor predictive of an advanced histological score was the HCV RNA level at the time of biopsy.

In studies published from Egypt reporting on living donor related liver (LDLT) transplantation of HCV-G4 patients, similar favorable outcomes were observed. Yosry et al. investigated the outcome of 74 Egyptian patients transplanted for HCV-G4. 31. 1% of patients developed HCV recurrence during a follow up period of 36 months. The majority of patients had mild recurrence, and 91% of the subjects had a fibrosis score of < or = F2. None of the transplanted patients developed cirrhosis or clinical decompensation. Recurrent hepatitis C virus infection was associated with a high pre and post-transplant viral load. The presence of antibodies to hepatitis B core antigen were also associated with disease recurrence [55]. In another study, recurrence was evaluated in 38 Egyptian patients infected with HCV-G4. Patient and graft survivals were 86.6% at the end of the 16 +/− 8.18 months (range, 4-35 months) follow-up period. Clinical HCV recurrence was observed in 10/38 patients (26. 3%). Similar to the previous study, none of the recipients developed cirrhosis or decompensation during the follow-up period [10]. Allam et al. compared the outcomes of Middle Eastern patients who received liver transplantation either in China or locally in Saudi Arabia, respective one- and three-year cumulative survival rates were 81% and 59% in patients transplanted in China compared with 90% and 84% for patients transplanted locally. The incidence of complications was significantly higher especially biliary complications, sepsis, metastasis and acquired HBV infection post-transplant in patients transplanted in China. Patients transplanted in Chine were more likely to undergo postoperative interventions and hospital admissions. This could be explained by the liberal recipient selection criteria, the use of donations after cardiac death, and to the limited post-transplant medical care [56].

HCV-G4 exhibits significant genetic diversity, and there are a number of viral subtypes. The impacts of the various subtypes have been demonstrated in recent studies; for example, HCV G1 subtype 1b patients were more likely to have a better post-transplant outcome compared with subtype 1a [57]. Studies performed in Egypt, where HCV-G4 subtypes 4a and 4b predominate, reveal a better antiviral treatment outcome compared with Saudi Arabia [58–60]. In a retrospective analysis of HCV-G4 patients, Roulot *et al*. reported better sustained virological response (SVR) in 4a subtype- compared with 4d subtype-infected individuals [61]. It is very important to point out the that the negative transplant outcome of HCV-G4 infected patients in the west is not accurate. The majority of recruited patients in these studies are older Egyptians, who have received marginal donor grafts. Co-morbidities, such as infection with schistosomiasis, and other unstudied variables may also have affected outcomes in these patients, leading to an impression that HCV-G4 is an aggressive virus. However, data originating from the Middle East, where HCV-G4 predominates, have revealed no significant difference in outcomes between G1 and G4.

More importantly the recent introduction of DAAs have changed the outlook for HCV-infected patients. The use of DAA agents in the liver transplantation setting has eliminated post-transplant HCV recurrence and improved graft and patient survival irrespective of many other factors including viral genotype.

3. Treatment of HCV in the peritransplant period

3.1 Pegylated interferon and ribavirin (RBV)

Viral eradication or suppression prior to liver transplantation reduces post-transplant recurrence rates [62]. Interferon-based therapy was the only treatment option for HCV prior to the DAA era, however, interferon was contraindicated in patients with advanced liver cirrhosis. This negatively impacted the HCV outcome in cirrhotic and organ transplant patients [63–65].

The limited treatment options lead multiple groups to carefully evaluate Interferon based therapy in the pre transplant setting. Everson *et al*. evaluated the effectiveness, tolerability, and outcome of a low accelerating dose regimen (LADR) of pegylated interferon (PEG-IFN) therapy in the treatment of patients with advanced HCV. This approach was poorly tolerated especially in patients with decompensated disease. One hundred twenty-four patients were treated with LADR, Sustained virological response was achieved in less than 25% and only 12/15 patients who became HCV-RNA negative prior to transplantation remained HCV-RNA negative 6 months after transplantation [64]. In a more recent study patient with various genotypes were randomized 2: 1 to treatment (n = 31) or untreated control (n = 16). Of the patients who were treated, 23 underwent liver transplantation, and 22% achieved a post-transplantation virological response. Although pre-transplant treatment prevented post-transplant recurrence in 25% of cases, including patients infected with HCV-G4, this approach was poorly tolerated and resulted in life-threatening complications [66]. With the introduction of DAA all trials and evaluating interferon based therapies were discontinued and interferon use in this setting is currently contraindicated.

Previously treatment options for patients with recurrent HCV after transplantation were limited. IFN based therapy for patients with post-transplant recurrence were the only available option in the past, these regimens are difficult to tolerate and have disappointing efficacy with hard-to-manage drug interactions. Reported SVR rates for PEG-IFN combination therapy following liver transplantation are lower than those in the nontransplant population. Treatment regimens have been hindered by a high incidence of adverse effects, leading to treatment withdrawal.

Dabbous *et al*. evaluated 243 patients transplanted for HCV-G4-related cirrhosis. Patients with proven histological recurrence received PEG-IFN and ribavirin. Repeated liver biopsies were performed at 3, 6, and 12 months during treatment for the detection of immune-mediated rejection induced by interferon. Histopathological disease recurrence was high 56 (23%), and 42 patients completed the treatment. Five patients were excluded due to fibrosing cholestatic hepatitis; therefore, 37 patients were included in the study. Erythropoietin and granulocyte colony-stimulating factor were used in 70% of patients. SVR was achieved in 29 (78%) patients [67]. Ponziani *et al*. evaluated treatment responses in 17 Italian patients with HCV-G4 recurrence following liver transplantation. The observed overall survival after LT was 100% at 1 year and 83. 3% at 5 years. Thirty-five percent of patients achieved SVR. This study included patients treated with conventional interferon; the lack of aggressive management of hematological side effects and the inclusion of patients with advanced liver disease contributed to the low response rate [68].

Al-hamoudi et al. assessed the safety and efficacy of PEG-IFN alpha-2a in combination with RBV in the treatment of recurrent HCV genotype 4 after LT. Pretreatment liver biopsies were obtained from all patients. Five patients had advanced pretreatment liver fibrosis. Only 14 (56%) patients achieved SVR. The most common adverse effects were flu-like symptoms and cytopenia. One patient developed severe rejection complicated by sepsis, renal failure, and death. Other adverse effects included depression, mild rejection, impotence, itching, and vitiligo [69].

4. Treatment of advanced disease in the new era

The treatment of chronic hepatitis C has been revolutionized with the introduction of DAAs. New oral DAAs have emerged with better safety and efficacy profiles, leading to dramatic changes in the practice of HCV management. The goal of HCV treatment is to reduce mortality and liver complications through virologic cure. The end point is sustained virological response (SVR), which is an undetectable viral load at least 12 weeks after completing treatment. The DAAs target various proteins throughout the HCV replication cycle [70]. These choices include sofosbuvir based therapy plus weight-adjusted RBV, ombitasvir/paritaprevir/ritonavir, elbasvir-grazoprevir and glecaprevir/pibrentasvir. The choice between them depends primarily on potential for drug interactions, availability, and cost. Data on the use of these new agents in cirrhotic G4 patients awaiting liver transplantation are limited. Up-to-date studies evaluating the safety and efficacy of these agents in HCV-G4 patients are summarized below.

4.1 Sofosbuvir and ribavirin

Sofosbuvir (SOF) is a novel pangenotypic nucleotide analog inhibitor that inhibits HCV RNA replication. SOF is administered orally and inhibits the HCV NS5B polymerase. SOF exerts potent antiviral activity against all HCV genotypes [71–75].

Curry et al. conducted a trial to determine whether sofosbuvir and RBV treatment before liver transplantation could prevent HCV recurrence afterward. They included 61 patients with child A cirrhosis and HCV of any genotype. All involved patients were on waitlists for liver transplantation for hepatocellular carcinoma and received up to 48 weeks of sofosbuvir (400 mg) and RBV before liver transplantation. Of 46 patients who were transplanted, 43 had HCV-RNA levels of less than 25 IU/ml at the time of transplantation. Of these 43 patients, 30 (70%) exhibited a post-transplantation virological response at 12 weeks [76]. Another study evaluated the efficacy and safety of SOF in combination with RBV in HCV-G4 patients in patients of Egyptian ancestry. 60 patients were included and half of them were treatment-naïve. Patients were treated for 12 weeks (n = 31) or 24 weeks (n = 29). Overall, 23% of patients had cirrhosis. SVR was achieved by 68% of patients in the 12-week group, and by 93% of patients in the 24-week group. Treatment was well tolerated and none of the patients discontinued treatment due to an adverse event [77]. Doss et al. evaluated the efficacy and safety of SOF in combination with ribavirin in HCV-G4 patients in Egypt. 103 patients were included and received a combination of SOF and weight-adjusted RBV. 17% of the study population were cirrhotic. Patients with cirrhosis at baseline had lower rates of SVR (63% at 12 weeks, 78% at 24 weeks) than those without cirrhosis (80% at 12 weeks, 93% at 24 weeks). The most common adverse events were fatigue, headache, insomnia, and anemia. Two patients experienced serious adverse events. No adverse events resulted in treatment discontinuation [78]. In a more recent study, 2400 Egyptian patients with liver cirrhosis due to chronic HCV infection were treated with SOF

and RBV for 24 weeks. The majority of included patients were treatment-naive. The overall SVR rate was 71. 2%. The most common adverse events were fatigue, myalgia, headache, insomnia, and anemia. Only 5.6% of patients discontinued treatment due to the appearance of significant complications [79]. In another study 14 409 patients received either dual therapy, SOF/RBV for 6 months (group1) or triple therapy with SOF/peg-IFN-alfa-2a/RBV for 3 months (group 2), in a cohort of patients treated in National Treatment Programme affiliated centres in Egypt. In group 1, the SVR at week 12 was 94% and in group 2 the SVR was 78.7% [80].

The efficacy of this combination following LDLT was also evaluated in Saudi Arabia. Ajlan et al. reported the safety and efficacy data on 36 post liver transplant patients who received SOF and RBV ± peg-IFN. All patients were infected with HCV-G4, mean age was 56 years, and the cohort included 24 males and one patient had cirrhosis. The majority of patients had advanced fibrosis. 28 patients were treated with PEG-IFN and RBV in addition to SOF for 12 weeks and the remaining were treated with SOF and RBV only for 24 weeks. By week 4, only four (11. 1%) patients had detectable HCV RNA [81]. In another study 39 Egyptian liver transplant recipients were treated for recurrent HCV-G4 after transplantation with SOF and ribavirin for 6 months. SVR was achieved in 76% of recipients. SVR was significantly higher in treatment-naïve patients and in recipients with a low stage of fibrosis [82]. A prospective multicenter study enrolled 40 patients with compensated recurrent HCV infection of any genotype following liver transplantation. All patients received 24 weeks of SOF 400 mg daily and RBV. Of the 40 patients enrolled and treated, 40% had biopsy proven cirrhosis, and 88% received prior interferon treatment. SVR was achieved by 28 of 40 patients. Relapse accounted for all cases of virological failure, including the only patient with HCV-G4. No deaths, graft losses, or episodes of rejection occurred. No interactions with any concomitant immunosuppressive agents were reported [83]. Forns et al. conducted a post-transplantation study in which SOF and RBV were provided on a compassionate-use basis to patients with severe recurrent HCV, including those with fibrosing cholestatic hepatitis (FCH) and decompensated liver cirrhosis with a life expectancy of less than one year. Patients received SOF and RBV for 24–48 weeks, PEG-IFN was added in some patients. The study population included patients infected with HCV- G4. The overall SVR rate was 59% and was higher (73%) in those with early severe recurrence. 123 serious adverse events occurred in 49 patients (47%). Severe adverse events associated with hepatic decompensation were the most frequent, with 26 adverse events occurring in 19 patients (18%) [84]. However, with the emergence of other treatment options this combination is not considered the best treatment option (**Table 2**).

4.2 Sofosbuvir/ledipasvir (LDV)

Colombo et al. evalaluated the safety and efficacy of LDV-SOF in kidney transplant recipients with chronic genotype 1 or 4 HCV infection and included patients with cirrhosis**.** Ten patients in this trial were infected with HCV-G4 and all included patients achieved SVR. Treatment with LDV-SOF for 12 or 24 weeks was well-tolerated and seemed to have an acceptable safety profile among kidney transplant recipients with HCV genotype 4 infection [85]. In a recently published study real-world effectiveness of LDV-SOF was evaluated. 135 patients infected with G4 were included, the overall SVR rate was 89.6% including treatment experienced and cirrhotic patients [86]. Charlton et al. (SOLAR-1) assessed treatment with LDV, SOF, and RBV in patients infected with HCV-G1 or HCV-G4. This study included a cohort of patients with cirrhosis who had not undergone liver transplantation. The SVR rate in the cirrhotic group was 86–89% [87]. Kohli et al. evaluated

Study	Sample size	Genotypes	SVR	Treatment protocol
Ajlan [81]	36	4	91.6%	SOF+RBV+PEG-INF for 12 weeks or SOF+RBV for 24 weeks
Dabbous [82]	39	4	76%	SOF+RBV 24 weeks
Forns [95]	104	1, 2, 3, 4	59%	SOF+RBV for 24–48 weeks
Abaalkhail [93]	50	4	86%	LDV-SOF+/-RBV 12-24 weeks
Mann [94]	227	1,4 (n=27)	92.5%	SOF+LDV+RBV 12-24 weeks
Dumortier [108]	125	All(11 G4)	92%	SOF/DCV+/-RBV 12-24 weeks
Coilly [107]	137	All (12 G 4)	96%	SOF+DAC
Leroy [102]	23 (all with FCH)	All (3 G4)	96%	SOF+DCV for 24 weeks
Reau [128]	100	All (3 G4)	100% for G4	Glecaprevir/Pibrentasvir for 12 weeks
Agarwal [131]	79	1,4 (n=4)	100% for G4	SOF/VEL

SVR = sustained virological response, SOF = sofosbuvir, RBV = ribavirin, LDV = ledipsavir, DCV = daclatasvir, SIM = simeprevir, FCH = fibrosing cholestatic hepatitis, Peg-INF = pegylated interferon.

Table 2.
Prospective studies that included HCV-G4 patients following liver transplantation.

12 weeks of combination therapy with LDV and SOV for patients with chronic HCV-G4 infections. 20 (95%) of 21 patients completed 12 weeks of treatment and achieved SVR (95% CI 76-100), including seven patients with cirrhosis. One patient was non-adherent to study drugs and withdrew from the study, but was included in the intention-to-treat analysis. No patients discontinued treatment because of adverse events [88]. Crespo et al. investigated the effectiveness and safety of DAAs in patients with HCV-G4 infection in routine practice. 130 patients with HCV-G4 were treated with LDV/SOV, SVR was achieved in 93. 2% of cirrhotic patients [89]. Abergel et al. also evaluated the efficacy and safety of therapy with LDV and SOF in patients with HCV-G4. Forty-four patients (22 treatments naïve and 22 treatment experienced) received a fixed-dose combination tablet of 90 mg LDV and 400 mg SOV orally once daily for 12 weeks. Ten patients (23%) had compensated cirrhosis. The SVR rate was 93% and was similar in treatment-naïve (95%, 21/22) and treatment-experienced (91%, 20/22) patients. Treatment was well tolerated with no serious adverse events [90]. Sanai et al. assessed real-world safety and efficacy of LDV/SOF with or without RBV in HCV-G4 infected patients with compensated and decompensated cirrhosis. This observational cohort (n = 213) included HCV-G4 treatment-naïve (59.6%) and -experienced (40.4%) patients with advanced fibrosis (F3, Metavir; n = 30), compensated (F4, n = 135) and decompensated cirrhosis (n = 48) treated for 12 (n = 202) or 24 weeks (n = 11) with LDV/SOF. RBV was dosed by physician discretion between 600 and 1200 mg daily. Patients with prior DAA failure were excluded from the analysis. Overall, 197 (92.5%) of the patients achieved SVR [91]. The SVR rate was as high as 98% for genotype 4 when using this combination to treat treatment-niave cirrhotic patients for 12 weeks [92]. Abaalkhail et al. evaluated prospectively the safety and efficacy of LDV-SOF for 12 to 24 weeks with or without RBV in treating HCV-4 infected patients with cirrhosis (cohort A) or post-liver transplantation (cohort B). A total of 111 patients (61 cirrhotic; 50 postliver transplants) with HCV genotype 4 were included. SVR was achieved in 91.8% and 86% of cohorts A and B, respectively. There were no treatment-related mortality or significant side effects [93].

Cohort B of the SOLAR-1 study enrolled patients who had undergone liver transplantation and included patients with post-transplant liver cirrhosis. Patients were randomly assigned to receive a fixed-dose combination tablet containing LDV and SOF plus RBV for 12 or 24 weeks. The cohort included 108 post-transplant patients. SVR was achieved in 96–98% of patients without cirrhosis or with compensated cirrhosis, in 85%–88% of patients with moderate hepatic impairment, in 60%–75% of patients with severe hepatic impairment, and in all six patients with FCH [87]. Similarly, an open-label study at 34 sites in Europe, Canada, Australia, and New Zealand evaluated treatment outcome in the pre and post-transplant settings. Cohort A included patient with cirrhosis who had not undergone liver transplantation. Cohort B included post-transplantation patients who had either no cirrhosis; CTP-A, CTP-B, or CTP-C cirrhosis; or fibrosing cholestatic hepatitis. Patients in each group were randomly assigned to receive 12 or 24 weeks of LDV (90 mg) and SOF (400 mg) once daily, plus RBV (600–1200 mg daily). The majority of patients were infected with HCV genotype 1 and only 37 were infected with genotype 4. Among all patients with genotype 4 HCV, SVR was achieved by 14 of 18 (78%) patients (12 weeks' treatment) and 16 of 17 (94%) patients (24 weeks' treatment) [94]. SOF/LDV combination was also evaluated in the post-transplant setting in a recently published German study that included both genotypes 1, 4. An overall SVR was achieved in 97% of patients [95].

The safety profile of LVD/SOF with RBV was evaluated in a pooled analysis of SOLAR-1 and -2 studies. These two studies included cirrhotic or post–liver transplantation patients infected with genotypes 1 and 4 and were randomized to 12 or 24 weeks of treatment. Treatment in the two trials was well tolerated and safe. RBV-associated anemia was the most common adverse effect, representing over 50% of reported drug-related adverse events [96].

4.3 Sofosbuvir/daclatasvir (DCV)

DCV is a pangenotypic NS5A inhibitor with a very low potential for drug interaction and a favorable safety profile. EL-khayat et al. investigated the efficacy and safety of SOF/DCV for treatment of patients with HCV-G4 induced cirrhosis. This was a multicenter study involving 551 patients with HCV-G4 related cirrhosis; 432 naïve patients and 119 treatment-experienced patients. All patients received SOF/DCV/RBV for 12 weeks and when RBV is contraindicated the treatment duration was extended to 24 weeks. SVR rate was 92% in naïve cirrhotic patients and 87% in previous treated patients [97]. In a French study, 176 HCV-G4 patients were treated with SOF and DCV. All the patients enrolled had advanced stages of liver fibrosis. The overall SVR rate was 90%, with the highest rate (97%) reached in cirrhotic patients treated with RBV, a the lowest (88%) in those treated without RBV [98]. In another recently published study involving only HCV-G4 patients, SVR was achieved in 100% of patients who received SOF/DCV with or without RBV. This study included patients with advanced fibrosis and cirrhosis. Adverse events occurred in 32% of patients, but none discontinued treatment [99]. The Phase II, open-label, nonrandomized IMPACT study assessed the efficacy of three DAAs (simeprevir, sofosbuvir, and daclatasvir) in HCV genotype 1/ 4-infected cirrhotic patients with portal hypertension or decompensated liver disease. All patients received simeprevir (SIM) 150 mg, DCV 60 mg, and SOF 400 mg once-daily for 12 weeks. All 40 patients included in the study achieved SVR and the combination was well tolerated [100]. The outcome of SOF/DCV/RBV in non-responders to prior sofosbuvir-based therapy was evaluated in a large Egyptian study that included 1014 patients in which 47% were cirrhotic. Overall SVR was 90.6% with no major side effects [101].

Multiple other studies showed high SVR rates among genotype 4 infected patients [102–106].

Data on the use of DCV in the post-transplant setting for HCV-G4-infected patients are limited.

In a multicenter prospective study 137 patients with post-transplant HCV recurrence received SOF and DCV. This cohort included 12 patients infected with HCV-G4. The SVR rate after completing treatment was 96% under the intention-to treat analysis. No clinically relevant drug–drug interactions were noted, but 52% of patients required a change to the dosage of immunosuppressive drugs [107]. A recent prospective multicenter study evaluating SOF based therapy in the post liver transplant setting was conducted and included all genotpes. The main combination regimen was SOF/DCV (73.6%). SVR was 92.8% (on an intent-to-treat basis) [108]. Leroy *et al*. analyzed data from 23 patients with FCH who participated in a prospective cohort study in France and Belgium to assess the effects of antiviral agents in patients with recurrence of HCV infection after liver transplantation. Three patients with G4 infection were included in this study and all 3 achieved SVR [109].

4.4 Sofosbuvir/Simeprevir (SIM)

SIM is a NS3/4A protease inhibitor with antiviral activity against G1, G2, G4, G5, and G6.

An open-label, multicentre, phase IIa study evaluated the outcome of SIM plus SOF for eight or 12 weeks in HCV-G4 infected patients. This study included 23 cirrhotic patients who received a 12 week course of therapy. Treatment comprised SIM 150 mg and SOF 400 mg daily. All cirrhotic patients achieved SVR and the treatment was well tolerated [110]. In a phase III, open-label, single-arm study the efficacy and safety of 12 weeks of SIM plus SOF in treatment-naïve and experienced HCV-G4 infection, including cirrhotic patients was conducted. All patients achieved SVR including the cirrhotic patients. No serious adverse events were reported and no patients discontinued study treatment [111]. The combination of SIM/SOF in a recently published Egyptian study involving genotype 4 infected patients resulted in a SVR rate of 92% in 100 treated patients [112]. The Phase II IMPACT study was conducted in HCV genotype 1- or 4-infected cirrhotic patients with portal hypertension or decompensated liver disease and assessed the combination of the three direct-acting antivirals SIM, DCV and SOF. All 40 patients achieved SVR [113]. Multiple other studies that included cirrhotic and treatment experienced patients treated with SIM and SOF revealed high SVR rates [114–116].

The efficacy and safety of SOF-based regimens in the real world among a cohort of Egyptian patients with recurrent HCV post LDLT was evaluated in HCV-G4 infected patients. 190 patients were included. Out of 190, 119 received SOF/RBV, 38 SOF/SIM, 22 SOF/DCV)/ ± RBV, and 11 received SOF/LDV/ ± RBV. SVR rates were as follow: 84.9% in SOF/RBV group, 94.7% in SOF/SIM, 100% in SOF/DCV, and 100% in SOF/LDV. Treatment was well tolerated with no significant drug–drug interactions [117]. The outcome of the combination SIM + SOF ± RBV in a group of liver transplant patients with HCV genotype 4 infection in Spain was evaluated in a real life study. This was a multicenter retrospective study, including 28 HCV genotype 4 patients from 11 liver transplant centers. The SVR was 95.23% including patients with advanced fibrosis and cirrhosis [118].

4.5 Ombitasvir, ritonavir and paritaprevir

The combination of ombitasvir, ritonavir and paritaprevir was evaluated in multiple studies involving compensated cirrhotic HCV-G4 patients and revealed high SVR rates reaching 100% in some studies [119–124]. In a recent meta-analyses, 20 cohorts across 12 countries were identified, totaling 5158 patients infected with

G1 and 4. The overall SVR rates were 98.9% for HCV-G4 infected patients [125]. The regimen is contraindicated in Child Pugh classes B and C cirrhosis, therefor its use in the pre transplant setting is limited.

4.6 Glecaprevir/Pibrentasvir

The EXPEDITION-1 trial enrolled 146 patients with compensated cirrhosis, 16 (11%) patients were infected with HCV-G4. Patients in this trial received a fixed dose of glecaprevir (300 mg)/pibrentasvir (120 mg) for 12 weeks. SVR was 100% for patients infected with HCV-G4 [126].

EXPEDITION-8 is a randomized trial that enrolled 343 patients with HCV Genotypes 1–6 and compensated cirrhosis. All patients received an 8-week course of Glecaprevir/Pibrentasvir. Of 343 patients, 13 had HCV-G4. The SVR12 rate in HCV-G4 was 100% [127].

On the other hand, MAGELLAN-2 trial was a phase 3, open-label trial for patients at least 3 months post transplantation. The study enrolled 100 patients of HCV. Three patients with genotype 4 underwent LT. After a 12-week course, all HCV-G4 infected patients achieved SVR 12 [128].

Immunosuppressive therapy should be monitored closely due to the possibility of drug–drug interaction when used with protease inhibitors.

4.7 Sofosbuvir/Velpatasvir (VEL)

In 2015, ASTRAL-1 evaluated the efficacy and safety of 12-week course of VEL and SOF. Of the 624 patients, 116 (19%) had genotype 4. One fourth of genotype 4 patients had cirrhosis. After a 12-week course of SOV/VEL, all patients (100%) with HCV-G4 achieved SVR [129].

ASTRAL-4 trial enrolled 267 patients with decompensated cirrhosis, CPT B. The study was open label with 3 arms that included: SOF/VEL for 12 weeks, SOF/VEL in addition to RBV for 12 weeks, or SOF/VEL for 24 weeks. In this trial, 8 (3%) patients had genotype 4. Regardless of the assigned arm, all genotype 4 patients (100%) achieved SVR. In this study, 81% of patients with MELD score above 15 had improvement after completion of treatment. This study was one of the earliest trials to evaluate SOV/VEL for decompensated cirrhotic patients [130].

In a recent trial 79 post liver transplant patients with HCV-G 1 and 4 received SOF/VEL daily for 12 weeks. In this trial, 4 patients were infected with HCV-G4. All patients with genotype 4 achieved SVR. There were no deaths or rejection episodes during the study period [131].

4.8 Sofosbuvir/Velpatasvir/Voxilaprevir (VOX)

POLARIS-1 trial assessed the safety and efficacy of SOF/VEL/VOX taken for 12 weeks vs. placebo. Patients with cirrhosis represented 46% of the study population. All patients with genotype 4 (22) were in the active treatment arm. By the end of the study period, 20 patients (91%) achieved SVR. One cirrhotic patient developed NS5A Y93H resistance-associated substitution and the other one did not receive treatment.

In the POLARIS-4 trial, patients were assigned to either SOF/VEL/VOX or SOF/VEL once daily for 12 weeks. All genotype 4 patients received SOF/VEL/VOX. The SVR rate was 100% for HCV-G4 infected patients [132].

The use of combined SOF/VEL/VOX is not recommended in patients with advanced liver disease CPT C. There are no currently strong data to support SOF/VEL/VOX use post liver transplantation. Case reports showed favorable outcome in the post-transplant setting [133].

4.9 Elbasvir/Grazoprevir (EBR/GZR)

A randomized controlled open label trial assessed the effectiveness of EBR/GZR with or without RBV for 12 or 16 weeks. The study population was 420 patients out of whom 36 had HCV-G4. The SVR for HCV-G4 patients was 89% which improved with a longer duration of treatment [134].

Jacobson et al. published the integrated analysis of 6 clinical trials. The analysis included 402 patients who received EBR/GZR once daily +/− RBV, for 12-18 weeks. Twenty-three patients with HCV-G4 were included in the analysis. Six patients were treatment naïve and they all achieved SVR. In the treatment experienced group, 4 patients (100%) achieved SVR after 16-18 week of treatment. However, the success rate was lower in treatment experienced patients with a 12-week course without RBV (66.7%) or with RBV (80%) [135].

Data for this combination in the post-transplant setting is limited.

4.10 DAA treatment failures

Despite the high SVR rate associated with DAA in HCV-G4 infected patients, a small percentage of patients do not respond to treatment. In the early era of DAA the most common approach was to add RBV or in some studies PEG-IFN and extend the treatment duration. However, with the emergence of new DAA choices, changing to another DAA became the most common approach. Yousif et al. conducted a prospective cohort study to assess the safety and efficacy of 12 weeks' retreatment with either combination of SOF/DCV/SMV/RBV (45 patients) or SOF/OBV/PTV/r/RBV (163 patients) in patients who had previously failed NS5A inhibitors-based regimens. The overall SVR rates in the two groups were 98. 1% [136]. In another study, patients who failed SOF/DCV were retreated successfully with other DAAs [137]. In a recently published study quadruple regimen of (sofosbuvir, daclatasvir, and simeprevir with a weight-based ribavirin) in chronic HCV-G4 DAAs-experienced patients was successful in eradicating the virus [138]. Multiple other studies revealed similar results [139, 140].

5. Timing of treatment for patients on the transplant list

The management of hepatitis C virus (HCV) infection in patients with decompensated cirrhosis has evolved dramatically. DAAs have shown to be safe and effective in patients with decompensated cirrhosis with high SVR rates. However, it is still debatable on when to initiate treatment in patients with advanced liver disease. Krassenburg et al. evaluated the impact of SVR in a large international multicenter cohort study, including a large number of patients with HCV-related cirrhosis treated with DAAs. Achievement of SVR was independently associated with a 2. 5-fold lower risk of cirrhosis-related complications or death in patients with compensated cirrhosis. On the other hand, no clinical benefit was apparent with HCV eradication in patients with decompensated liver disease. Among patients with CP-B/C cirrhosis, the event-free survival and LT-free survival did not differ between those with SVR and those without SVR. Furthermore, MELD score improvement did not translate to a beneficial clinical outcome in these subset of patients. Thus, DAA therapy may lower prioritization for LT through MELD score reduction, which is likely to primarily affect those with a more urgent need liver transplantation [141]. Other recently published studies assessed the impact of DAAs on patients awaiting liver transplant. They evaluated whether patients can be first inactivated due to clinically improvement and subsequently delisted in a real

life setting. Treated patient had a significant improvement in the median MELD and Child Pugh score. They concluded that all oral DAAs were able to reverse liver dysfunction and may result in delisting of about 20-30% of patients. Patients with lower MELD scores had higher chances to be delisted. However, the longer term benefits of therapy need to be ascertained [142, 143]. Similarly, Afdahl et al. evaluated the outcome of DAA in compensated and decompensated cirrhotic patients. They also measured the hepatic venous pressure gradient before and after treatment in fifty patients with Child-Pugh-Turcotte (CPT) A and B cirrhosis and portal hypertension. They observed a clinically meaningful improvement in portal hypertension in addition to improvements in liver biochemistry, Child–Pugh score and Model for End-Stage Liver Disease scores [144]. The potential benefits of treating patients on the waiting list include potential improvements in overall clinical status that may salvage these patients from liver transplantation; reducing post-transplant recurrence; and avoiding possible post-transplant drug–drug interactions. One concern is that treating these patients may lower their MELD scores and drive them down the transplant list, thus delaying transplantation despite persistent portal hypertensive complications.

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