Chapter 5

Management of Hepaitits C Virus Genotype 4 in the Liver Transplant Setting

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Additional information is available at the end of the chapter

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Abstract

End-stage liver disease secondary to hepatitis C virus (HCV) infection is the major indication for orthotopic liver transplantation (OLT) worldwide. It also has a negative impact 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 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 the leading indication for liver transplantation (LT) and is a major cause of liver-related mortality [1, 2]. It also has a negative impact on patient and graft survival leading to an inferior transplant outcome when compared with other indications [3, 4].

HCV eradication prior to LT will likely improve the outcome by eliminating the risk of post transplant recurrence. In the absence of an effective HCV vaccine to prevent infection and with therapy until very recently limited to interferon (IFN)-based regimens, most HCV-infected candidates for LT patients remained untreated.

Hepatitis C genotype 4 (HCV-G4) is the most prevalent genotype in the Middle East and Northern Africa [5–8]. The frequency of infection with HCV-G4 is also increasing in European countries, particularly among intravenous drug users [9–12]. The most common genotype in Europe and the USA is genotype 1; therefore, HCV-G4 has not been adequately studied in prospective trials evaluating treatment outcomes and remains the least studied variant.

The impact of HCV-G4 on treatment outcomes in the general nontransplant population has been evaluated [13–18]. Studies from the Middle East suggest a higher rate of spontaneous resolution after acute HCV-G4 infection [19, 20]. Other studies suggest that HCV-G4 infection is associated with significant steatosis. These observations suggest that specific features of HCV-G4 infection may contribute to the natural history and treatment outcomes of the disease [21, 22].

The percentage of HCV-G4 patients among recipients of orthotopic liver transplantation (OLT) varies depending on the geographic location. HCV-G4 represents more than 90% of indications for liver transplantation in Egypt [23]. In Saudi Arabia, hepatitis C represents ~29% of indications for liver transplantation, ~60% of which are secondary to HCV-G4 [24]. On the other hand, HCV-G4 is a relatively uncommon indication for liver transplantation in Europe and North America [25, 26].

Until recently, interferon-based therapy was the only treatment for HCV. However, this treatment has its own drawbacks given its prolonged therapeutic course (24–48 weeks), numerous side effects, low barrier to resistance, and reduced efficacy in prior null responders or cirrhotic patient. 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 (SVR) 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 [27]. 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. Multiple clinical studies have shown superiority of sofosbuvir (SOF)-based therapy when compared with the current standard of care in both treatment naïve and treatment experienced patients and across all HCV genotypes [28–34]. Because of its favorable pharmacologic profile and its reasonable drug–drug interactions, sofosbuvir has become the cornerstone in the management of HCV infection [35]. Furthermore, data are emerging on the outcome of multiple newer agents. 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.

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2. Hepatitis C genotype influences post-liver transplantation

Campos-Varela et al. evaluated the role of the various HCV genotypes on the progression and outcome of liver transplantation. Among 745 recipients, 81% had genotype 1 (G1), 7% had genotype 2 (G2), and 12% had genotype 3 (G3). Patients were followed for a median of 3.1 years (range 2–8 years). The risk of advanced fibrosis and graft rejection was significantly higher among those infected with G1 compared with other genotypes [36]. In another multicentre European study involving 652 liver recipients, genotype 1b, age, and absence of pretransplantation coinfection by HBV are risk factors for recurrent HCV. However, graft and patient survival was comparable to other genotypes [37]. Similarly, in another prospective study involving 60 liver transplant recipients, HCV 1b was associated with more aggressive recurrent liver disease than other genotypes [38]. Gordon et al. assessed the relationship between hepatitis C genotype on posttransplant frequency of recurrent hepatitis, histologic severity of recurrence, and progression to cirrhosis. They concluded that histologic evidence of recurrent hepatitis C is seen in 90% of liver allografts; however, genotype 1b was associated with more severe histologic disease recurrence and was more likely to progress to cirrhosis when compared to non-1b genotypes [39].

By contrast, some large studies have observed no difference in the rate or degree of hepatitis or in graft or patient survival between G1 and other genotypes [40, 41]. Therefore, the impact of various genotypes on the outcome of liver transplantation remains controversial. Due to the low prevalence of HCV G-4 in western countries, these studies neglected evaluating the impact of this particular genotype.

3. Natural history of HCV-G4 after liver transplantation

Re-infection of the graft is universal after liver transplantation regardless of genotype, leading to an accelerated course of liver injury in many cases [42]. Most studies of disease recurrence worldwide have investigated HCV-G1, HCV-G2, and HCV-G3, and there are few reports on post-OLT recurrence of HCV-G4.

Zekry et al. analyzed factors that predicted outcome of HCV-liver transplant recipients in the Australian and New Zealand communities. The following variables were evaluated demographic factors, coexistent pathology at the time of transplantation, HCV genotype, and donor age. In this analysis, 182 patients were transplanted for HCV including 16 patients infected with genotype 4 and the median follow-up was 4 years. Among many factors studied in univariate and multivariate analyses, HCV-G4 was associated with an increased risk of retransplantation and death. Additionally, patients infected with HCV-G4 were more likely to progress to advanced stages of fibrosis [43]. Patients infected with G2 and G3 had better posttransplant outcomes. 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. 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. A group of 149 patients with HCV infection who received liver transplants 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. Among the patient population, 14 patients were infected with HCV-G4. Approximately 50% of these patients 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. The authors speculated that patients infected with G1b had an increased replicative potential and an increased expression of viral antigen in liver tissue. A more detailed 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 patients, 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 5-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. The HCV-G4 groups were predominantly Egyptian patients who received organs from older donors. Furthermore, the majority of these patients were placed on an alternative waiting list to be offered organs that were suitable for transplantation but unsuitable or not needed for citizens of the UK. 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.

Factors affecting transplant outcome
Viral load
Genotype
Coinfections
Alcohol
Compliance
Steatosis
Donor age
Immunosuppression
Rejection

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

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 3-year graft and patient survival rates of 90 and 80%, respectively [24, 46–50]. Similarly, in Egypt, where many active living-related liver transplant programs exist and HCV-G4 represents more than 90% of cases, graft and patient survival rates are ~86% [23].

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Multiple recent studies from the Middle East evaluated the natural history of HCV-G4 following liver transplantation. Mudawi et al. conducted a study to determine the epidemiological, clinical and virological characteristics of patients with biopsy-proven recurrent HCV infection and analyzed the factors that influence recurrent disease severity. They also compared disease recurrence and outcomes between HCV-4 and other genotypes [51]. Of 116 patients who underwent OLT for hepatitis C, 46 (39.7%) patients satisfied the criteria of recurrent hepatitis C. Twenty-nine (63%) patients were infected with HCV genotype 4. 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. The conclusion was that HCV recurrence following OLT in HCV-4 patients is not significantly different from its recurrence for other genotypes.

In studies published from Egypt reporting on living donor related liver (LDLT) transplantation of HCV-G4 patients, similar favorable outcomes were observed. In a recent Egyptian study 74 adult hepatitis C virus positive subjects were monitored for 36 months after living-donor liver transplant and demographic and laboratory data for the recipients and donors were evaluated. HCV clinical recurrence was observed in 31% of patients and was mostly mild; 91% of patients had fibrosis scores less than F2. And during the study period 91% of patients were alive with excellent graft function. Similar to the study from Saudi Arabia, recurrent HCV was associated with a high pre- and post-transplant viral load and the presence of antibodies to hepatitis B core antigen [52]. In another study, the outcome of LDLT was evaluated in Egyptian patients with HCV-G4-related cirrhosis. Recurrence of HCV was studied in 38 of 53 adult patients who underwent LDLT. Recipient 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%). None of the recipients developed allograft cirrhosis during the follow-up period [23]. In a recent study, Allam et al. compared the outcomes of Saudi and Egyptian patients who received liver transplantation either in China or locally in Saudi Arabia (~30% infected with HCV-G4), respective 1- and 3-year cumulative survival rates were 81 and 59% in patients transplanted in China compared with 90 and 84% for patients transplanted locally. They attributed the poorer outcomes in patients transplanted in China to liberal selection criteria, the use of donations after cardiac death, and to the limited post-transplant care [53].

The role of HCV-G4 in the natural history of this disease requires further study. Furthermore, 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 achieve a rapid virological response (RVR) compared with subtype 1a [54]. Studies performed in Egypt, where HCV-G4 subtypes 4a and 4b predominate, have consistently indicated higher rates of virological response to therapy (69–76%) compared with Saudi Arabia, where response rates are substantially lower (44–50%) [55–57]. 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 [58]. The majority of patients involved in these European/Australian studies are Egyptians, who are likely older, have coexisting HCC and have received marginal donor grafts. Co-morbidities, such as infection with schistosomiasis, and other nonstudied variables may also have affected

outcomes in these patients, leading to an impression that HCV-G4 is an aggressive virus. However, more recent studies originating from the Middle East, where HCV-G4 predominates have revealed no significant difference in outcomes between G1 and G4.

4. Treatment prior to transplantation

4.1. Pegylated interferon and ribavirin

Viral eradication or suppression prior to liver transplantation reduces post-transplant recurrence rates [59]. Until recently, the only available treatment regimens were interferon-based and were therefore contraindicated in patients with advanced cirrhosis [60–62].

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. One hundred twenty-four patients were treated with LADR. Sixty-three percent had clinical complications of cirrhosis (ascites, spontaneous bacterial peritonitis, varices, variceal hemorrhage, encephalopathy). Forty-six percent were HCV RNA-negative at end of treatment, and 24% were HCV RNA-negative at last follow-up. Twelve of 15 patients who were HCV RNA-negative before transplantation remained HCV RNA-negative 6 months or more after transplantation. They concluded that LADR may result in viral eradication, stabilize clinical course, and prevent posttransplantation recurrence [61]. In a more recent study patients with various genotypes were randomized 2:1 to treatment (n = 31) or untreated control (n = 16). Of the 30 patients who were treated, 23 underwent liver transplantation, and 22% achieved a post-transplantation virological response. Although pre-transplant treatment prevented post-transplant recurrence of HCV infection in 25% of cases, including patients infected with HCV-G4, this approach was poorly tolerated and resulted in life-threatening complications [63].

5. Treatment of advanced disease in the new era

The treatment of HCV patients is rapidly evolving. New oral DAAs have emerged with better safety and efficacy profiles, leading to dramatic changes in the practice of HCV management. These choices include sofosbuvir plus weight-adjusted ribavirin (RBV), ledipasvir/sofosbuvir with or without RBV, sofosbuvir/daclatasvir with or without RBV, daclatasvir/simeprevir/sofosbuvir, ombitasvir/paritaprevir/ritonavir with weight-adjusted RBV, elbasvir-grazoprevir with or without RBV. 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.

5.1. 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 [28–30, 32, 64].

In a recently published open-label study, 61 patients with HCV of any genotype awaiting liver transplantation for hepatocellular carcinoma were included. The primary end point was the proportion of patients with HCV-RNA levels <25 IU/ml at 12 weeks after transplantation among patients with this HCVRNA level at their last measurement before transplantation. Patients received up to 48 weeks of SOF/RBV before liver transplantation. Of 46 patients who were transplanted, 43 had HCV-RNA levels of <25 IU/ml at the time of transplantation. Of these 43 patients, 30 (70%) exhibited a post-transplantation virological response at 12 weeks [65]. A recently published study evaluated the efficacy and safety of SOF in combination with RBV in HCV-G4 patients in patients of Egyptian ancestry. Thirty treatment-naive and thirty previously treated patients were enrolled and treated for 12 weeks (n = 31) or 24 weeks (n = 29). Overall, 23% of patients had cirrhosis. SVR12 was achieved by 68% of patients in the 12-week group, and by 93% of patients in the 24-week group. No patient discontinued treatment due to an adverse event [66]. In another Egyptian study, 103 patients' studies were treated with a combination of SOF and weight-adjusted RBV. Seventeen percentage of the study population were cirrhotic. Patients with cirrhosis at baseline had lower rates of SVR12 (63% at 12 weeks, 78% at 24 weeks) than those without cirrhosis (80% at 12 weeks, 93% at 24 weeks). However, the treatment was safe and well tolerated, with no serious drug-related adverse events [67].

However, with the emergence of other treatment options, this combination is not considered the best treatment option.

5.2. Ledipasvir/sofosbuvir and ribavirin

A recently published phase 2, open-label study (Solar-1) assessed treatment with ledipasvir (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 and another cohort of patients who had undergone liver transplantation. In the nontransplant cirrhotic group, SVR12 was achieved in 86–89% of patients. There were no differences in response rates in the 12- and 24-week groups [68]. In another study, 20 (95%) of 21 patients infected with HCV-4 completed 12 weeks of treatment and achieved SVR12 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 [69].

5.3. Sofosbuvir/daclatasvir/ribavirin

The ALLY-1 study evaluated daclatasvir (DCV) + SOF + RBV in patients with advanced cirrhosis or post-transplant HCV recurrence of all genotypes, including G4. DCV is a pangenotypic NS5A inhibitor with a very low potential for drug interaction and a favorable safety profile. All patients with advanced cirrhosis were treated with a combination of DCV 60 mg +

S0F 400 mg + RBV (adjusted dose) for 12 weeks. Overall, 83% of the advanced cirrhosis patients achieved SVR12. SVR12 rates were higher in patients with Child-Pugh class A or B, 93%, versus class C, 56%. The response rate of cirrhotic patients infected with HCV-G4 (4 patients) was 100%. Treatment was well tolerated, with no adverse events or drug-drug interactions [70].

5.4. Simeprevir/daclatasvir/sofosbuvir

The interim results of the IMPACT study indicated favorable responses to this combination in cirrhotic patients infected with G1 and G4. Simeprevir (SIM) is a NS3/4A protease inhibitor with antiviral activity against G1, G2, G4, G5, and G6. All cirrhotic patients (100%) 28/28 achieved SVR4. The treatment was safe and well tolerated, with no major adverse effects. The study is ongoing, and final results will be reported later [71]. A recent report from Qatar has examined the efficacy and safety of Sofosbuvir/daclatasvir and Sofosbuvir/Simeprevir on 85 patients. SVR4 was achieved in 96% of the study population [72].

5.5. Ombitasvir, ritonavir and paritaprevir

The combination of ombitasvir, ritonavir and paritaprevir was evaluated in a large cohort of non cirrhotic genotype-4 patients. After 12 weeks of treatment, 100% of naïve patient who had RBV containing regimen achieved SVR compared to 90.9% in the RBV free regimen. Furthermore, all treatment experienced patients achieved SVR [73]. This combination when used with RBV was also found very effective in HCV genotype-4 with compensated (child A) cirrhosis. Twelve and 16 weeks of treatment resulted in SVR12 of 97 and 100%, respectively [74]. This regimen in addition to dasabuvir was also effective in cirrhotic genotype 1b patient. SVR 12 was 100% in 60 compensated cirrhotic patients [75]. The regimen is contraindicated in Child Pugh classes B and C cirrhosis. More recently, an open-label, partly randomised trial in patients with chronic HCV genotype 4 infection was conducted in Egypt. One hundred and sixty patients were included; 100 patients were assessed as not having cirrhosis and were given 12 weeks of treatment, and 60 patients assessed as having cirrhosis were randomly assigned to the 12-week treatment group (n = 31) or the 24-week treatment group (n = 29). Ninety-four (94%) of 100 patients in the without cirrhosis group, 30 (97%) of 31 patients in the cirrhosis 12-week treatment group, and 27 (93%) of 29 patients in the cirrhosis 24-week treatment group achieved SVR12. Adverse events were predominantly mild or moderate in severity, and laboratory abnormalities were not clinically meaningful. No patients discontinued treatment because of an adverse event [76].

5.6. Elbasvir/grazoprevir

In a recent study, an SVR rate of 96% was achieved in 56 treatment-naïve patients receiving 12 weeks of elbasvir-grazoprevir. In contrast, SVR rates were lower with only 12 weeks among a small number of treatment-experienced patients (78% in 9 patients) but were higher with the addition of ribavirin and treatment extension to 16 weeks (100% in 8 patients). SVR rates were similar in patients with and without cirrhosis. However, this regimen is contraindicated in Child Pugh classes B and C cirrhosis [77].

5.7. Sofosbuvir/velpatasvir

Sofosbuvir and velpatasvir (NS5A inhibitor) is a pangenotypic combination that was recently evaluated in the ASTRAL-1 trial that included 624 naïve and treatment experienced patients, of whom 116 (19%) were genotype-4. Patients with compensated cirrhosis (19%) were included and all genotype-4 patients achieved SVR (100%) after 12 weeks of RBV-free treatment [78]. A phase 3 open-label study involving patients infected with HCV genotypes 1 through 6 who had decompensated cirrhosis was recently conducted. Patients were randomly assigned in a 1:1:1 ratio to receive sofosbuvir and velpatasvir once daily for 12 weeks, sofosbuvir-velpatasvir plus ribavirin for 12 weeks, or sofosbuvir-velpatasvir for 24 weeks. Overall rates of sustained virologic response were 83% among patients who received 12 weeks of sofosbuvir-velpatasvir, 94% among those who received 12 weeks of sofosbuvir-velpatasvir plus ribavirin, and 86% among those who received 24 weeks of sofosbuvir-velpatasvir [79].

6. Treatment after liver transplantation

Earlier studies on preemptive treatment prior to established disease recurrence were disappointing. The conclusion of these studies was that the outcome of preemptive treatment was similar to that of controls in terms of histological recurrence, graft loss, and death [80, 81]. Treatment regimens in these studies were interferon based which resulted in poor tolerability, renal impairment, cytopenias, and drug interactions. DAAs have revolutionized the management of HCV infection in the posttransplant setting. Recent clinical trials have shown high sustained virologic response rates, shorter durations of treatment, and decreased adverse events when compared with the previous PEG-INF based therapy. However, most of these studies were performed in HCV-G1-infected patients. Data on treating HCV-G4 recurrence following liver transplantation are limited (**Table 2**).

6.1. Pegylated interferon and ribavirin

Reported SVR rates for pegylated interferon 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. All patients had a protocol biopsy 6 months post-transplant. Patients received PEG-IFN and ribavirin in case of histological recurrence. Repeated liver biopsies were performed at 3, 6, and 12 months during treatment for the detection of immune-mediated rejection induced by interferon. Fifty-six (23%) patients had evidence of histopathological disease recurrence, and 42 patients completed the treatment. Five patients were excluded due to fibrosing cholestatic hepatitis (FCH); therefore, 37 patients were included in the study. The patients received treatment in the form of combined PEG-IFN and RBV. Erythropoietin and granulocyte colony-stimulating factor were used in 70% of patients. SVR was achieved in 29 (78%) patients. The high SVR rate in this study was attributed to several factors, including the early treatment protocol, exclusion of patients with fibrosing cholestatic hepatitis and aggressive treatment of hematological

Study	Sample size	Genotypes	SVR	Treatment protocol
Ajlan [88]	36	4	91.6%	SOF + RBV + PEG − INF for 12 weeks or SOF + RBV for 24 weeks
Dabbous [27]	39	4	76%	SOF + RBV for 24 weeks
Charlton [89]	40	All (1 genotype 4)	70%	SOF + RBV for 24 weeks
Forns [90]	104	1, 2, 3, 4	59%	SOF + RBV for 24–48 weeks
Abergel [91]	44	4	93%	SOF + LDV for 12 weeks
Charlton [68]	108	1 and 4	96–98% in compe nsated cirrhosis 85–88% in cirrhosis with mild hepatic dysfunction 60–75% in cirrhosis with severe hepatic dysfunction	SOF + LDV + RBV for 12–24 weeks
Manns [92]	227	1(200) and 4(27)	92.5% of genotype 4 patients	SOF + LDV + RBV for 12–24 weeks
Dumortier [94]	125	All (11 genotype 4)	92%	Predominant SOF/daclatasvir ± RBV
Coilly [95]	137	All (12 genotype 4)	96%	SOF + daclatasvir (DAC)
Leroy [97]	23 (all with FCH)	All	96%	SOF + DCV for 24 weeks

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.

complications [82]. Conversely, in the largest series reported from Europe, 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. However, this retrospective study included patients treated in the 1990s with conventional interferon; the drug tolerability, the lack of aggressive management of hematological side effects and the inclusion of patients with advanced liver disease contributed to the low response rate [83]. In a recent study from Saudi Arabia, 25 patients infected with HCV-G4 were treated with PEG-IFN alpha-2a and RBV [84].

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Pretreatment liver biopsies were obtained from all patients. Biochemical and virological markers were assessed before, during, and after treatment. Five patients had advanced pretreatment liver fibrosis. Eighty-eight percent achieved an early virological response; of those, 15 (60%) and 14 (56%) patients achieved end of treatment virological response and SVR, respectively. The most common adverse effects were flu-like symptoms and cytopenia. Eighteen patients (72%) required erythropoietin alpha and/or granulocyte-colony stimulating factor as a supportive measure. One patient developed severe rejection complicated by sepsis, renal failure, and death. Other adverse effects included depression, mild rejection, impotence, itching, and vitiligo. The relatively high response rate in this study may have been due to the treatment-naïve status of the patients, the use of growth factors that allowed patients to complete their course of therapy, the low treatment-withdrawal rate, and the reduction in immunosuppressive therapy during treatment.

The results of these studies suggest that post-transplant treatment outcomes for HCV-G4 are likely better than for G1 and less favorable than for G2 and G3. This response pattern among the different genotypes parallels the response pattern in the immunocompetent population. The availability of newer treatment options with better safety profiles is drawing attention away from PEG-IFN and RBV.

7. HCV treatment in the new antiviral era

7.1. Telaprevir and boceprevir

Following the approval of telaprevir (Incivek™) and boceprevir (Victrelis™) for G1 treatment outcomes improved [85, 86]. Treatment regimens for chronic HCV-G1 infection include a combination of either of these protease inhibitors three times daily with once-weekly subcutaneous injections of PEG-IFN and twice-daily oral RBV. These new combinations increased SVR to 80% and 63–66%, respectively, in nontransplant patients. Some studies have reported poor clinical outcomes of the use of telaprevir and PEG-IFN in patients with HCV-G4 [87]. Burton et al. conducted a retrospective cohort study of 81 patients with genotype 1 HCV treated with boceprevir (10%) or telaprevir (90%) plus PEG-IFN and RBV at six US transplant centers (53% stage 3–4/4 fibrosis, 57% treatment experienced). The intent-to-treat SVR12 rate was 63%. Adverse effects were common; 21% of patients developed anemia (hemoglobin < 8 g/dl) and 57% required blood transfusions during the first 16 weeks. Twenty-seven percent were hospitalized and 9% died; all were liver-related [88]. Although the use of these two DAAs in post–liver transplant patients resulted in SVR up to 60% with telaprevir, nonresponders were observed in the boceprevir treatment, and it was associated with severe side effects, including severe anemia that required erythropoietin, RBV dose reduction and red blood cell transfusions. Significant drug interactions also occurred with immunosuppressants, requiring average cyclosporine dose reductions of 50–84% after telaprevir initiation and 33% after boceprevir initiation. Tacrolimus doses were reduced by 95% with telaprevir [27]. These significant side effects coupled with the introduction of safer antiviral drugs have shifted HCV

treatment away from these agents; in fact, these agents are contraindicated by many liver association.

7.2. Sofosbuvir and ribavirin

SOF has become a cornerstone of the management of HCV infection because of its favorable pharmacological and drug interaction profiles. However, there are very limited data on the use of SOF in patients with HCV recurrence post–liver transplant, particularly G4. Ajlan et al. conducted an open label prospective cohort study at a tertiary care hospital in Saudi Arabia. The primary endpoint was SVR12 in patients treated with sofosbuvir-based therapy in post-liver transplant patients with genotype 4 HCV recurrence. Thirty-six treatment-experienced liver transplant patients with HCV recurrence received sofosbuvir and ribavirin with or without PEG-INF. The majority of patients had ≥stage 2 fibrosis. Twenty-eight 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. Of the 36 patients, two (5.5%) relapsed and one died (2.75%) [89]. Another recent study evaluated the efficacy, safety, and tolerability of SOF and RBV in LDLT recipients with recurrent HCV-4. In this study Thirty-nine Egyptian LDLT recipients were treated for recurrent HCV after LDLT with SOV and RBV without PEG-IFN for 6 months. Thirty eight patients completed 24 weeks of treatment and were followed for 12 weeks after end of treatment. One patient died during the first week of treatment. SVR was achieved by 76% (29/38) of recipients. SVR was significantly higher in treatment-naïve patients and in recipients with a low stage of fibrosis. Only two patients developed severe side effects wile on treatment in the form of severe pancytopenia and acute renal failure [90]. A recent prospective multicenter study enrolled 40 patients with compensated recurrent HCV infection of any genotype after a primary or secondary 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% had been previously treated with interferon. SVR12 was achieved by 28 of 40 patients. Relapse accounted for all cases of virological failure, including the only patient with HCV-G4. The most common adverse events were fatigue (30%), diarrhea (28%), and headache (25%). In addition, 20% of the subjects experienced anemia. No deaths, graft losses, or episodes of rejection occurred. No interactions with any concomitant immunosuppressive agents were reported [91]. A recent post-transplantation study was conducted 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 <1 year. Data from the first 104 patients who completed or prematurely discontinued treatment were included. All patients received SOF and RBV for 24–48 weeks. Investigators were allowed to add PEG-IFN to the regimen at their discretion. 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. At the end of the study, 57% of patients displayed clinical improvement, 22% were unchanged, 3% had worsened clinical status, and 13% had died. Overall, 123 serious adverse events occurred in 49 patients (47%). Serious adverse events associated with hepatic decompensation were the most frequent, with 26 adverse events occurring in 19 patients (18%) [92].

7.3. Sofosbuvir/ledipasvir with or without ribavirin

Abergel evaluated the efficacy and safety of therapy with LDV and SOF in patients with HCV genotype 4. Forty-four patients (22 treatment 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. Among study participants, HCV genotype 4 subtypes were well represented (4a, n = 25; 4d, n = 10; other subtypes, n = 9). Ten patients (23%) had compensated cirrhosis. All 44 patients completed the full 12 weeks of treatment. The SVR12 rate was 93% and was similar in treatment-naïve (95%, 21/22) and treatment-experienced (91%, 20/22) patients. The three patients who did not achieve SVR12 had virological relapse within 4 weeks of the end of treatment; all three had a high baseline HCV RNA, a non-CC IL-28B genotype, and pretreatment NS5A resistance-associated variants. None of the patients experienced a serious adverse event [93].

Cohort B (of the previously described Solar-1 study) enrolled patients who had undergone liver transplantation and included patients with various degrees of disease severity. 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. SVR12 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. Response rates were also similar in the 12- and 24-week groups [68]. An open-label study at 34 sites in Europe, Canada, Australia, and New Zealand recruited two groups of patients, cohort A included patients with Child-Turcotte-Pugh class B (CTP-B) or CTP-C 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 (1:1) using a computer-generated randomisation sequence to receive 12 or 24 weeks of LDV (90 mg) and SOF (400 mg) once daily, plus ribavirin (600–1200 mg daily). Of 333 patients who received treatment, 296 had genotype 1 HCV and 37 had genotype 4 HCV. Among all patients with genotype 4 HCV, SVR12 was achieved by 14 of 18 (78%) patients (12 weeks treatment) and 16 of 17 (94%) patients (24 weeks treatment). Of the five patients who did not achieve SVR12, three—all receiving 12 weeks of treatment—had virological relapse, and two died (one post-transplantation CTP-A on 12 weeks of treatment, and one untransplanted CTP-C on 24 weeks of treatment) and were not included in the analysis. Twenty five of twenty seven HCV-G4 in cohort B of the study achieved SVR the only two relapsers were cirrhotics [94]. Despite including G1 and G4 in these studies, the number of HCV-G4 infected patients was relatively small, limiting solid conclusions on the response of HCV-G4.

The safety profile of LVD/SOF with RBV was evaluated in a pooled analysis of two large multicenter studies (Solar-1 and -2). The patients involved were either cirrhotic or post–liver transplantation patients (616 G1 and 42 G4) and were randomized to 12 or 24 weeks of treatment. Of 134 SAEs, only 20 were related to treatment. RBV-associated anemia was the most common adverse effect, representing 11/20 (55%) of reported drug-related adverse events [95].

7.4. Sofosbuvir/daclatasvir

Data on the use of DCV in the post-transplant setting for HCV-G4-infected patients are limited. A prospective multicenter cohort including patients with HCV-recurrence following LT treated with second generation direct antivirals was conducted. The aim of the t study was to assess efficacy and tolerance of sofosbuvir (SOF)-based regimens for the treatment of HCV recurrence in patients with severe fibrosis after LT. A SOF-based regimen was administered to 125 patients including patients infected with HCV-G4 (11 patients). The main combination regimen was SOF/DCV (73.6%). SVR12 was 92.8% (on an intent-to-treat basis); seven cases of virological failure were observed including 1 HCV-G4 patient treated with SOF/daclatasvir (DAC) combination [96]. In another multicenter prospective study137 patients with HCV recurrence receiving SOF and DCV, were included whatever the genotype or fibrosis stage. This cohort included 12 patients infected with HCV-G4. The primary efficacy end point was a sustained virological response 12 weeks after the end of treatment. The SVR rate 12 weeks after completing treatment was 96% under the intention-to treat analysis and 99% when excluding non-virological failures. Only two patients experienced a virological failure. The serious adverse event rate reached 17.5%. Four patients (3%) stopped their treatment prematurely because of adverse events. Anaemia was the most common adverse event, with significantly more cases in the RBV group. No clinically relevant drug–drug interactions were noted, but 52% of patients required a change to the dosage of immunosuppressive drugs [97]. Fontana et al. in a retrospective multicenter study evaluated daclatasvir (DAC)/SOF combination post liver transplantation in established HCV recurrence including HCV-4 patients. Eighty seven percent of patients achieved SVR and the treatment was well tolerated [98]. 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 (one patient was treated with SOF/RBV, and two were treated with SOF/DCV). All patients survived without re-transplantation. Rapid and dramatic improvements in clinical status were observed. The patients' median bilirubin concentration decreased from 122 μmol/L at baseline to a normal value at week 12 of treatment. Twenty-two patients (96%) had a complete clinical response at week 36, and 22 patients (96%) achieved SVR12, including all 3 patients infected with G4 [99].

7.5. Sofosbuvir and simeprevir

Data on the use of SIM for HCV-G4 recurrence following liver transplantation are limited to a small number of case reports and case series. In a recent report, three patients with HCV-G4 recurrence following liver transplantation were treated with SOF and SIM for 12–24 weeks. All three had high pretreatment viral loads, and one patient had established cirrhosis. SVR12 was achieved in all three patients, with no significant adverse effects or drug interactions [100]. Obed A et al. reported a patient with a recurring HCV-G4 infection and fibrosing cholestatic hepatitis following liver retransplantation, who was successfully treated with a combination therapy of SIM and SOF without PEG-INF/RBV [101].

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8. 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 (**Figure 1**). Many factors may contribute to and affect the approach on an individual basis; for example, it may be better to defer treatment in extremely ill patients. Belli et al. assessed the impact of DAAs on patients awaiting liver transplant. They evaluated whether patients can be first inactivated due to clinicall improvement and subsequently delisted in a real life setting. They included 103 consecutive listed patients without hepatocellular carcinoma who were treated with different DAA combinations in 11 European centers. Treated patient had a significant improvement in the median model for end-stage liver disease (MELD) and Child Pugh score. They concluded that all oral DAAs were able to reverse liver dysfunction and favoured the inactivation and delisting of about one patient out-of-three and one patient out of- five in 60 weeks, respectively. Patients with lower MELD scores had higher chances to be delisted. However, the longer term benefits of therapy need to be ascertained [102]. Similarly Afdhal et al. evaluated the outcome of treatment with SOF and RBV in compensated and decompensated cirrhotic patients. They also monitored the clinical picture and measured the hepatic venous pressure gradient before and after treatment. 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 [103]. The potential benefits of treating patients on the waiting list include potential improvements in overall clinical status that may salvage these patients from liver transplan-

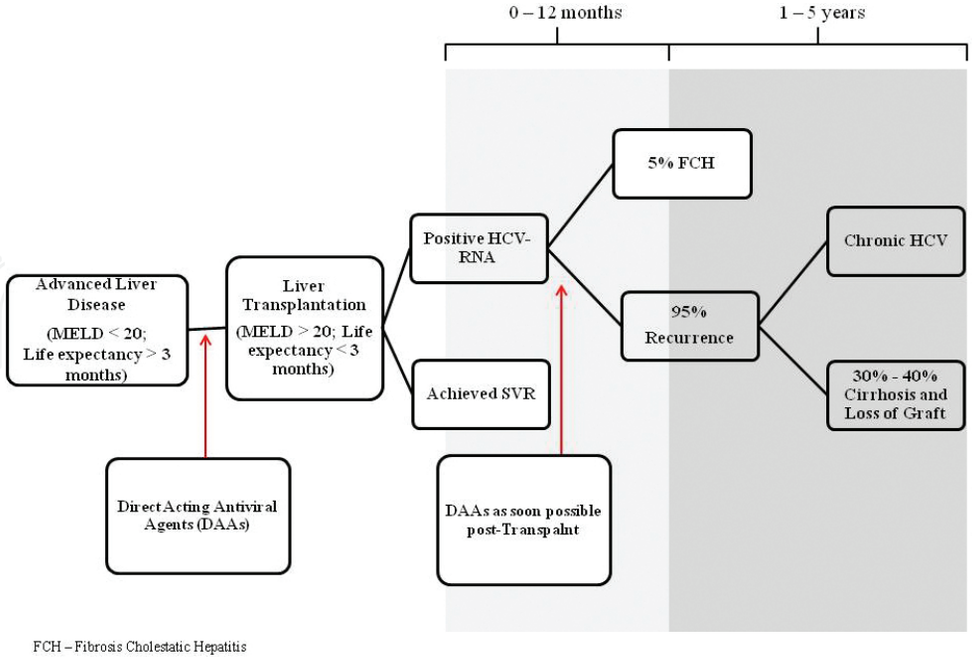

Figure 1. Post transplant natural history of HCV recurrence with potential treatment strategies.

tation; 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. The decision to treat HCV in patients with decompensated cirrhosis should be individualized till short and long term outcome data become available.

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