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REVIEW

Use of direct-acting agents for hepatitis C virus-positive kidney transplant candidates and kidney transplant recipients

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SUMMARY

In some parts of the world, hepatitis C virus (HCV) infection remains a huge problem for kidney transplant candidates and kidney transplant (KT) recipients. Until 2 years ago, anti-HCV treatment for the general population relied on pegylated alpha-interferon plus ribavirin, but led to a sustained viral response (SVR) in <50% of cases. This treatment was contraindicated in KT patients because of acute-rejection issues and was poorly tolerated in patients with end-stage renal disease (ESRD). Over the last year, direct-acting antiviral agents (DAAs) have entered the market and are associated in the general population with a SVR of >90%, whatever the patient's HCV genotype. In KT patients, sofosbuvir-based therapy is associated with a SVR at nearly 100% in patients with a HCV genotype-1 infection, with almost no side effects and only mild interference with immunosuppressive drugs. Most HCV(+) patients with ESRD are genotype 1: in that setting, a recent study reported that the association of grazoprevir/elbasvir 100/50 mg/day led to a SVR of nearly 95% with very few side effects. Thus, it is concluded that DAAs can be safely used and lead to results in KT candidates and KT patients that are as good as those observed in the nonrenal population.

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Introduction

Chronic hepatitis C virus (HCV) infection remains a major health problem worldwide, high incidence in some countries, such as Egypt. Chronic HCV infection can result in end-stage liver disease, which may require liver transplantation and also harbors the risk of hepatocellular carcinoma. Apart from its impact on the liver, chronic HCV infection may also have systemic effects, such as autoimmune thyroiditis, lichen planus, cryoglobulinemia and glomerulonephritis [1]. In most cases, this is membranoproliferative glomerulonephritis, but can also be membranous glomerulonephritis [2]. HCV-related glomerulonephritis can result in end-stage renal disease (ESRD), despite antiviral therapy. Moreover, in the setting of hemodialysis, sporadic acute hepatitis C infection may occur [3], that is, nosocomial transmission, which in most cases evolves into chronic HCV infection [4].

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Thus, in the hemodialysis facilities of many countries, the prevalence of chronic HCV infection can be very high, that is, >50% of the dialysis population [5]. Some of these patients are kidney transplant candidates; hence, it has been shown that (i) HCV(+) hemodialysis patients have a significantly lower survival rate compared to hemodialysis patients who are HCV seronegative [6], (ii) survival of HCV(+) hemodialysis patients is significantly higher if they have the opportunity to receive a kidney transplant, compared to those who remain on hemodialysis [7], and (iii) survival of HCV (+) kidney transplant patients is significantly lower in the long-term compared to those who are HCV seronegative [8–10].

Until 2013, treatment of chronic HCV infection was based on pegylated alpha-interferon (Peg αIFN) plus ribavirin, which produced a sustained virological response (SVR) in 30–60% of patients, according to HCV genotype. However, due its elimination route, ribavirin is contraindicated for patients where estimated glomerular filtration (eGFR) rate is <50 ml/min [11]. Thus, HCV(+) dialysis patients have been excluded from receiving this dual therapy; however, two randomized controlled published trials have recently compared Peg αIFN as a monotherapy to Peg αIFN plus low-dose ribavirin (off-label use) given to hemodialysis patients [12,13]: they found that the addition of ribavirin to alpha-interferon doubled the rate of long-term SVR. With regard to HCV(+) kidney transplant patients, anti-HCV therapy has been contraindicated because Peg αIFN has immunomodulation properties, thereby triggering the onset of acute rejection, which in most cases is vascular [14,15].

In this review, we first examine current HCV treatments using direct-acting antiviral agents (DAA) given to patients with normal renal function and then report on this therapy given to patients with chronic kidney disease (CKD) and waiting for a kidney transplant, or given to HCV(+) kidney transplant patients.

Direct-acting anti-agents for patients with normal renal function

Direct-acting antiviral agents have recently been released onto the market. There are numerous types and they have different modes of action: the combination of at least two different classes can result in a SVR rate of >95%. Thus, they have dramatically changed the field of chronic HCV infection. Currently, DAAs [16,17], such as sofosbuvir, ledipasvir, daclatasvir, simeprevir, and ombitasvir, combined with paritaprevir and boosted with ritonavir, are associated with an increased SVR and are the gold standard for treating HCV infection in the general population [18,19] (Table 1). This is also true for cirrhotic patients: a SVR was found in 85.9% of cirrhotic patients who were Child-PughA and in 82.2% who were Child-PughB and C [20,21].

Sofosbuvir, a pangenotypic nucleotide analog inhibitor of HCV RNA-dependent RNA polymerase, was the first to be approved at more than a year ago. After this, simeprevir, a second-wave first-generation NS3-4A protease inhibitor that is active against genotypes 1 and 4, was approved, as were daclatasvir and ledipasvir, which are pangenotypic NS5A inhibitors. In addition, ombitasvir, an inhibitor of the HCV NS5A protein, and paritaprevir, aNS3/4A protease inhibitor, have shown antiviral activity against multiple HCV genotypes, including 1a and 1b. Paritaprevir is administered with the pharmacokinetic enhancer ritonavir, which inhibits metabolism, thus increasing peak trough levels and overall drug exposure, allowing once-daily intake [17]. In phase-III trials, a combination of these drugs [18,19], with or without ribavirin, was shown to be effective and well tolerated in treatment-naive and treatment-experienced noncirrhotic patients with HCV infection. Indeed, infection has been cured in more than 99% of genotype-1 HCV patients (Table 2), with a SVR generally associated with resolution of liver disease in patients without cirrhosis. However, efficacy is lower for genotype-3 infections; currently, HCV genotype-3 is the most difficult genotype to treat with the currently available DAAs (Table 3). The available options for each genotype in the general population are described in Table 2.

No dose adjustment of DAAs is required for patients with moderate renal impairment. However, the safety of different combinations of DAAs has not yet been assessed in patients with severe renal impairment (eGFR < 30 ml/min/1.73 m^2) or ESRD that requires hemodialysis. Simeprevir, daclatasvir and a combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir are cleared by the liver and can be used in patients with severe kidney disease. Sofosbuvir alone or associated with ledipasvir should not be administered to patients with an eGFR of <30 ml/min/1.73 m^2 or with ESRD until more data become available.

The need to adjust doses of approved HCV DAAs for patients with impaired renal function or on dialysis is as yet unknown for some of them because: very few safety dosing and efficacy data are available for this population: Table 1 summarizes the current evidence. Recent trials with new drugs [22,23] will change the

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Table 1. Available direct-acting antiviral drugs for patients with HCV infection.

Drug	Tablet dosage	Daily dose	Patients with CKD (eGFR < 30 ml/min)	Removal by dialysis?
Sofosbuvir	400 mg	One tablet/day	↗AUC in dialysis patients (by 451%) Can be used in CKD patients with cautious. Data are needed	Yes. To be administered after dialysis session
Simeprevir	150 mg	One tablet/day	Exposure increases with ↘ GFR Label states "can be used all across grades of renal impairment." Cautious	No
Daclatasvir	60 or 90 mg	One tablet/day	PK in dialysis patients is similar to that of patients with normal renal function	No
Sofosbuvir+ ledipasvir	Sofosbuvir 400 mg + ledipasvir 90 mg	One tablet/day	PK of ledipasvir is similar in patients with severe renal impairment to that of healthy volunteers	Unknown
Velpatasvir + Sofosbuvir	Velpatasvir 100 mg + Sofosbuvir 400 mg	One tablet/day	Can be used in CKD patients with cautious. Data are needed	Unknown
Paritaprevir/ritonavir + ombitasvir	Paritaprevir 75 mg + ritonavir 50 mg + ombitasvir 12.5 mg	Two tablets/day	No dose adaptation	Removed
Dasabuvir	250 mg	Two tablets/day	No dose adaptation	Unknown
Asunaprevir	100 mg	Two tablets/day	No dose adaptation	Unknown
Grazoprevir/elbasvir	Grazoprevir 100 mg/elbasvir 50 mg	One tablet/day	No dose adaptation	Grazoprevir: negligible Elbasvir: no

CKD, chronic kidney disease; PK, pharmacokinetic; GFR, glomerular filtration rate.

Table 2. Antiviral therapy in the general population with HCV genotype 1.

HCV genotype 1	Therapy	Weeks
Naïve	Sofosbuvir + ledipasvir	12
	Sofosbuvir + daclatasvir	12
	Sofosbuvir + simeprevir (G1b)	12
	Paritaprevir/r + ombitasvir + dasabuvir (G1b)	12
Prior failure to Peg-IFN + ribavirin	Sofosbuvir + ledipasvir	12
	Sofosbuvir + daclatasvir	12
	Sofosbuvir + simeprevir (G1b)	12
	Paritaprevir/r + ombitasvir + dasabuvir (G1b)	12
Compensated cirrhosis		
Naïve	Sofosbuvir + ledipasvir + ribavirin	12
	Sofosbuvir + daclatasvir	24
	Sofosbuvir + daclatasvir + ribavirin	12
	Sofosbuvir + ledipasvir	24
	Paritaprevir/r + ombitasvir + dasabuvir + ribavirin	12
	Paritaprevir/r + ombitasvir + dasabuvir + ribavirin (G1b with previous failure)	12
Decompensated cirrhosis		
Naïve or prior failure, Peg-IFN + ribavirin	Sofosbuvir + ledipasvir + ribavirin	12
	Sofosbuvir + daclatasvir	24
	Sofosbuvir + daclatasvir + ribavirin	12
	Sofosbuvir + ledipasvir	24

treatments for HCV in patients with CKD. Grazoprevir, an NS3/4A protease inhibitor, and elbasvir, a NS5A protein inhibitor of HCV, have shown antiviral activity against HCV genotype 1, 4, and 6 infections [22]. Phase-1 studies have found that less than 1% of grazoprevir and elbasvir are renally excreted and that dose adjustments of grazoprevir or elbasvir are not needed in the setting of nondialysis-dependent stages 4–5 CKD and dialysis-dependent stage 5 CKD.

Treatment of HCV infection in kidney transplant candidates

The use of ribavirin is contraindicated for ESRD patients when eGFR declines below 50 ml/min. Before the availability of DAAs, HCV RNA(+) dialysis patients were offered antiviral therapy when an acute HCV infection occurred, and those with chronic HCV infection and candidates for a kidney transplantation were offered antiviral therapy before being placed on a waiting list for a transplant kidney. In Europe and Japan, most HCV(+) hemodialysis patients have a 1a or 1b genotype [24]. Whatever the HCV genotype, the sustained virological rate with αIFN is ~30% and that of Peg αIFN is ~40–50%. However, two recent studies on naïve genotype-1 HCV(+) hemodialysis patients from Taiwan have shown that the association of Peg αIFN plus very low-dose ribavirin resulted in a SVR of ~60% [12,13].

DAA therapy for patients with end-stage renal disease

C-Surfer was the first randomized [23] placebo-controlled phase-III study to evaluate an all-oral, ribavirin-free regimen for patients with CKD stages 4/5. A total of 224 patients with HCV genotype 1 and CKD 4/5 ± hemodialysis were randomized to receive grazoprevir/elbasvir 100/50 mg (n = 111) or a placebo for 12 weeks. The mean SVR for all subjects who received grazoprevir/elbasvir was 94.6%. Once-daily grazoprevir/elbasvir, given for 12 weeks, was highly effective and resulted in a low number of adverse events in patients with advanced kidney disease and having HCV genotype 1 infection.

Saxena *et al.* [25] reported on 73 patients with an eGFRof ≤45 ml/min and treated with sofosbuvir (400 mg/day) in association with ribavirin (800 mg/day); of these, 83% of patients achieved a SVR. However, compared to patients that had an eGFR of >45 ml/min, those with an eGFR of ≤45 ml/min had higher rates of anemia, worsened renal function and serious adverse events, regardless of the use of ribavirin.

Nazario *et al.* [26] reported on a small cohort of 17 HCV(+)/RNA(+) patients with ESRD or impaired renal function (i.e., eGFR < 30 ml/min): of these, 47% were cirrhotic. Their DAA therapy relied on sofosbuvir (400 mg/day) plus simeprevir (150 mg/day), given for

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Table 3. Antiviral therapy in the general population with HCV genotypes 2, 3, 4, 5, and 6.

HCV genotype 2	Therapy	Weeks
Noncirrhotic		
Naïve	Sofosbuvir + ribavirin	12
Prior failure	Sofosbuvir + ribavirin	12
	Sofosbuvir + daclatasvir	12
Cirrhotic		
Naïve	Sofosbuvir + ribavirin	12
Prior failure	Sofosbuvir + ribavirin	24
	Sofosbuvir + daclatasvir	12
HCV genotype 3	**Therapy**	**Weeks**
Noncirrhotic		
Naïve or prior failure	Sofosbuvir + daclatasvir	12
	Sofosbuvir + Velpatasvir	12
Compensated cirrhosis		
Naïve or prior failure	Sofosbuvir + Peg-IFN + ribavirin	12
	Sofosbuvir + daclatasvir + ribavirin	24
Decompensated cirrhosis		
Naïve or prior failure	Sofosbuvir + daclatasvir + ribavirin	24
HCV genotype 4	**Therapy**	**Weeks**
Noncirrhotic		
Naïve or prior failure	Sofosbuvir + simeprevir	12
	Sofosbuvir + daclatasvir	12
	Sofosbuvir + ledipasvir	12
	Paritaprevir/r + ombitasvir + ribavirin	12
	Grazoprevir + elbasvir	12
Compensated cirrhosis		
Naïve or prior failure	Sofosbuvir + simeprevir + ribavirin	12
	Sofosbuvir + simeprevir	24
	Sofosbuvir + daclatasvir + ribavirin	12
	Sofosbuvir + daclatasvir	24
	Sofosbuvir + ledipasvir + ribavirin	12
Decompensated cirrhosis		
Naïve or prior failure	Sofosbuvir + daclatasvir + ribavirin	12
	Sofosbuvir + daclatasvir	24
	Sofosbuvir + ledipasvir + ribavirin	24
HCV genotypes 5 or 6	**Therapy**	**Weeks**
Naïve or prior failure	Sofosbuvir + ledipasvir	12
	Sofosbuvir + daclatasvir + ribavirin	12
	Sofosbuvir + daclatasvir	24
	Sofosbuvir + ledipasvir + ribavirin	12

12 weeks. The SVR at 12 weeks after completing treatment was 100%. Hundemer *et al.* [27] reported on a small series of six HCV(+)/RNA(+) patients with ESRD, of which three were cirrhotic. All patients received a sofosbuvir-based therapy. One patient had to stop treatment prematurely; for the other five patients, the SVR at 12 weeks after completing therapy was 67%. Finally, very recently Desnoyer *et al.* reported on the pharmacokinetic profile of two different doses of sofosbuvir in 12 hemodialysis patients (400 mg/day or 400 mg three times a week). Plasma concentrations of sofosbuvir or its inactive metabolite sofosbuvir-007 did not accumulate with either regimen between hemodialysis sessions or throughout the treatment course. In one patient receiving the once-daily regimen, sofosbuvir-007 half-life was slightly higher (38 h) than for patients with normal renal function receiving a full dose. Clinical and biological tolerance was good for all patients. Two relapses occurred with the three times a week regimen and none with the once-daily [28].

More, recently, reports from Japan show that the combined use of daclatasvir (60 mg/day) plus asunepre-vir (100 mg b.i.d.) given to HCV(+) genotype-1 dialysis patients, with or without cirrhosis, achieved a very high rate of SVR (i.e., >90%) [29–32].

In a recent studies, patients with HCV(+)/RNA(+) ESRD, that is, six with an eGFR of between 15 and 30 and 14 with eGFRs < 15 ml/min, were offered a 12-week treatment of ombitasvir formulated with pari-taprevir and ritonavir (25/150/100 mg/day), plus dasabuvir (250 mg b.i.d.). Those with genotype 1a (n = 13) also received ribavirin (200 mg/day). The rate of SVRs at 12 weeks was 90%; however, ribavirin had to be stopped in 9 of the 13 patients, demonstrat-ing that ribavirin in this population was not effec-tive [33].

Because HCV infection in patients with CKD is associated with an increased risk of all-cause and liver-related mortality, particularly in those who are suitable candidates for renal transplantation, DAAs could be considered as an antiviral therapy at the place of alpha-interferon plus ribavirin. However, patients with CKD who are given DAAs need careful monitoring for any comorbid conditions and drug-to-drug interactions.

Anti-viral HCV treatment with DAAs should be con-sidered for the following patients with CKD.

1. Those who are candidates for a kidney transplant, whatever the stage of liver fibrosis.
2. Those with chronic renal insufficiency what so ever the degree of liver fibrosis.
3. Those with chronic renal insufficiency and extrahep-atic manifestations related to cryoglobulinemia.

Treatment of HCV infection after kidney transplantation

HCV infection has a harmful effect after kidney transplantation. The survival of kidney transplant patients is significantly lower for HCV-positive RNA-positive patients compared to those that are HCV-negative [34]. This increased risk of death is mainly associated with cardiovascular disease, post-transplant diabetes mellitus, infections, and cancers [34]. HCV infection has been identified as an independent predictive factor for post-transplant diabetes mellitus [35], mainly in patients receiving a tacrolimus-based therapy [36].

Kidney allograft survival is also significantly lower in HCV-positive patients compared to those that are HCV-negative [37,38]. Graft loss is mainly related to *de novo* or relapsing HCV-associated glomerulonephritis, such as membrano-proliferative glomerulonephritis with or without cryoglobulinemia, and membranous glomerulonephritis [39]. HCV infection could be a risk factor for acute rejection; however, there are no robust data to confirm this association [40].

The impact of HCV replication on liver fibrosis after kidney transplantation is also controversial. Some studies have reported increased progression of liver fibrosis in this setting. However, other studies have shown that progression of liver fibrosis is only increased in some patients, whereas it remains stable for several years in others [41–43]. The difference between these studies is probably related to the different immunosuppressive regimens, that is, with or without calcineurin inhibitors (CNIs), azathioprine versus mycophenolic acid, and the type of induction therapy. Similar to immuno-competent patients, the risk of hepato-cellular carcinoma exists in transplant patients: hence, HCV infection has a harmful impact after kidney transplantation.

Unfortunately, until very recently, there was no efficient and safe therapy for HCV infection after kidney transplantation [11] Interferon-based therapy has a relative contraindication after kidney transplantation: it promotes acute rejection through its immune-stimulatory effects [14,15]. Peg αIFN therapy has been only given to patients that present with fibrosing cholestatic hepatitis [43]. Ribavirin alone [44,45], amantadine alone [46], or the combination of both has no impact on HCV replication [47]. Hence, KDIGO guidelines recommend that all HCV-positive candidates for a kidney transplant are treated before transplantation [11]. Indeed, it has been shown that, in cases where a SVR is obtained after treating HCV-positive hemodialysis, no relapse is observed after kidney transplantation, despite patients receiving a polyclonal antibody-induction therapy [48]. In addition, no HCV RNA is detected in mononuclear cells within the peripheral blood of these patients after transplantation [49]. It has been also shown that pretreatment of HCV infection before transplantation is associated with less progressive liver fibrosis [50] and less HCV-associated glomerulonephritis, even in the absence of HCV clearance [51].

Within the last couple of years, the use of new-generation DAA agents, that is, sofosbuvir combined with daclatasvir, simeprevir, or ledipasvir, with or without ribavirin, have been highly efficient at treating HCV infection in cirrhotic and noncirrhotic immuno-competent patients [17,52–55], and liver transplant patients [56–59]. The first report on the use of new-generation DAAs in the setting of kidney transplantation described a combined liver–kidney transplant patient who developed fibrosing cholestatic hepatitis after transplantation [60]. At that time, daclatasvir, simeprevir, and ledipasvir were not yet commercialized. Hence, this patient was given Peg αIFN, ribavirin, and sofosbuvir for 6 months. Virological clearance was rapidly observed, and a 12-week SVR was obtained [60].

Within the last few months, there have been reports on the use of DAAs given to HCV(+) kidney transplant patients. Our group reported on the efficacy and safety of a sofosbuvir-based therapy to treat HCV infection after kidney transplantation [61]. Twenty-five kidney transplant patients were given new DAAs. Ten had advanced liver fibrosis (F3 and F4 Metavir score) and the remaining 15 patients had mild liver fibrosis (F1/F2 Metavir score) and either HCV-associated extrahepatic manifestations or a history of graft loss caused by HCV-associated glomerulonephritis. Most patients (20 of 25) were infected with HCV genotype 1. Estimated GFR was 64 ± 21 ml/min/1.73 m^2. All patients had a GFR of >30 ml/min/1.73 m^2. Initial HCV RNA concentration was 6.33 ± 0.6 log IU/ml. Due to the progressive availability of new DAAs on the market, different antiviral regimens could be used. Patients were given sofosbuvir plus ribavirin (n = 3); sofosbuvir plus daclatasvir (n = 4); sofosbuvir plus simeprevir, with (n = 1) or without ribavirin (n = 6); sofosbuvir plus ledipasvir, with (n = 1) or without ribavirin (n = 9); and sofosbuvir plus pegylated-interferon plus ribavirin (n = 1). Antiviral therapy was given for 12 (n = 19) or 24 weeks (n = 6). At week 4 after starting a therapy, HCV RNA was undetectable in 22 of the 25 patients (88%). At the end of therapy and 12 weeks after the end of therapy, all 25 patients had undetectable HCV RNA. Hence, the SVR at 12 weeks was 100% [61]. Eight patients had

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impaired kidney function, but there were no acute-rejection episodes and no graft losses. However, tacrolimus trough level was significantly decreased after HCV clearance [61].

In a single-center study, Sawinski *et al.* [62] reported on 20HCV(+)/RNA(+) patients with a kidney transplant and treated with a DAA-based therapy, without interferon alpha. Three of these patients also received ribavirin. Of the 20 patients, 88% were infected by genotype 1 and 50% had biopsy-proven advanced hepatic fibrosis. DAA therapy was initiated at a median of 888 days after kidney transplantation. All 20 patients achieved SVR at 12 weeks after completing therapy. The treatment was well tolerated and less than half of the patients needed calcineurin-inhibitor dose adjusted during DAA therapy [62].

Recently, Lin *et al.* [63] pooled the data from three centers, totaling 24 kidney transplant recipients, of which 42% had advanced fibrosis or cirrhosis, and 58% were genotype 1a. Twelve patients were treated with sofosbuvir plus simeprevir: three of these also received ribavirin, eight received sofosbuvir plus ledipasvir (one of these eight patients also received ribavirin), and four patients received ribavirin alone. Treatment duration was 12 or 24 weeks according to various clinical and virological parameters. The SVR at 12 weeks was 91%; the two failures occurred in cirrhotic patients, which were subsequently successfully treated with other DAAs. Finally, there was no significant change in calcineurin-inhibitor trough levels either during or after the DAA-based treatments [63].

Recently, Colombo *et al.* [64] reported on a ledipasvir/sofosbuvir (90/40 mg) trial in 114 HCV (+) kidney transplant patients of genotypes 1 or 4. They compared ledipasvir/sofosbuvir for 12 or 24 weeks. They found that SVR4 rate was 100% in both arms. There were no safety issues.

HIV/HCV co-infected kidney transplant recipients can also benefit from DAA therapy. Very recently, Sawinski *et al.* [65] reported on six such patients who were all genotype 1. The patients were given ledipasvir plus sofosbuvir for 12 weeks: the SVR12 was 100%. However, tacrolimus dosing required adjustment during (a decrease in tacrolimus daily dose was needed for four patients) and after (increase in daily tacrolimus in three patients) this DAA treatment, but the antiretroviral regimens did not. In our experience, we have observed that, after HCV clearance, we need to increase daily tacrolimus dose in order to maintain trough levels similar to those at pre-DAA therapy [61].

Indeed, HCV is known to alter the pharmacokinetics of cyclosporine [66]. Very recently, Badri *et al.* [67] reported on a pharmacokinetic study that examined the interactions between ombitasvir, paritaprevir/ritonavir, and dasabuvir (3D), plus the CNIs tacrolimus and cyclosporin. They concluded that the "observed data for tacrolimus and cyclosporin in liver transplant recipients confirm that the recommended dosing strategies are valid and therapeutic levels of immunosuppression can be maintained during 3D treatment." Bearing this in mind, we recommend that calcineurin-inhibitor levels are closely monitored during and within the weeks following DAA therapy.

Many studies have been published on DAA therapies given to HCV(+) patients and those with normal renal function. However, further larger studies on DAA-based therapies are needed that focus on patients with ESRD and those with a kidney transplant to confirm these data.

In conclusion, DAA therapy has revolutionized the field of chronic hepatitis C infection, achieving SVR rates of greater than 90%. Some of these DAAs, such as simeprevir, daclatasvir, and a combination of ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir, can be given to patients with ESRD. However, as yet, we have no data from ESRD patients regarding the efficacy of other DAAS. In the near future, once-daily grazoprevir/elbasvir for 12 weeks will become a very effective antiviral therapy for patients with advanced kidney disease and a HCV G1 infection. The use of DAAS for both ESRD and kidney transplant recipients can achieve a SVR comparable to that obtained in nonrenal patients. DAAs will definitively change the long-term outcomes of HCV-positive kidney transplant patients.

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Conflict of interest

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