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# Treatment With Grazoprevir/Elbasvir for Renal Transplant Recipients With Chronic Hepatitis C Virus Infection and Impaired Allograft Function

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**Background.** Direct-acting antiviral agents are highly efficient treatment options for chronic hepatitis C virus (HCV) infection after renal allograft transplantation. Treatment options for patients with impaired graft function remain limited. Therefore, we assessed the effectiveness and safety of grazoprevir/elbasvir therapy for patients with chronic HCV infection and impaired renal allograft function. **Methods.** Eleven renal allograft recipients with therapy-naïve HCV genotype (GT) 1a, 1b, or 4 were treated with the fixed-dose combination of elbasvir/grazoprevir without ribavirin for 12 weeks. All recipients exhibited impaired graft function with an average glomerular filtration rate lower than 30 mL/min per 1.73 m<sup>2</sup>. Clinical data were retrospectively reviewed for renal and liver function parameters. Patients were closely monitored for trough levels of immunosuppressive agents, viral load, laboratory values, and potential adverse effects. **Results.** Seven (64%) patients exhibited a rapid virologic response within 4 weeks (HCV GT1a, n = 2; HCV GT1b, n = 5). The other 4 patients exhibited a virologic response within 8 weeks (HCV GT1b, n = 3; HCV GT 4, n = 1). All patients exhibited a sustained virologic response at week 12 after the end of treatment. Clinical measures of liver function improved substantially for all patients. Few adverse effects were reported. Impaired renal allograft function and proteinuria remained stable. For most patients, only moderate adjustments to the tacrolimus dosage were necessary for maintaining sufficient trough levels. **Conclusions.** This treatment appears to be safe and effective for renal transplant recipients with impaired allograft function and is a promising treatment option for eradicating HCV infection in this patient population.

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The introduction of interferon-free treatment regimens based on direct-acting antiviral agents (DAAs) has fundamentally changed treatment options for transplant patients with chronic hepatitis C virus (HCV) infection. Until recently, the remaining challenges associated with DAA treatment after solid organ transplantation (SOT) were impaired kidney function and drug-drug interactions (DDIs) with immunosuppressive substances. In particular, there were concerns

about the use of protease inhibitors after SOT because some of them were found to significantly impair trough levels of immunosuppressants after liver transplant.<sup>1,2</sup> Therefore, administering simeprevir or paritaprevir in conjunction with cyclosporine A is not recommended.<sup>3</sup> Sofosbuvir-based regimens are not recommended for patients with a glomerular filtration rate (GFR) lower than 30 mL/min per 1.73 m<sup>2</sup>, and the 3-drug regimen paritaprevir/ritonavir/ombitasvir plus

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dasabuvir is not the first choice because of DDIs with immunosuppressants and other medications. As a consequence, treating HCV infection after kidney transplant remains a problem, particularly when graft function is impaired.

Since August 2016, another regimen has been available for the treatment of patients chronically infected with HCV genotype (GT)1 or GT4 and a GFR lower than 30 mL/min per 1.73 m<sup>2</sup>: the protease inhibitor grazoprevir (GZR) in combination with the nonstructural protein 5A (NS5A) inhibitor elbasvir (EBR). However, although the current consensus statement of the European Liver and Intestine Transplant Association states that GZR/EBR should not be administered together with cyclosporine, only limited data are available regarding their use after SOT.<sup>4,5</sup>

In the retrospective study reported here, we reviewed the medical records of 11 kidney transplant recipients with impaired graft function who were treated for HCV infection with the fixed-dose combination of GZR/EBR. We carefully monitored trough levels of immunosuppressants, as well as kidney and liver function. Here we describe the excellent effectiveness and safety of this interferon-free, ribavirin (RBV)-free fixed-dose combination of GZR/EBR as treatment for chronic HCV infection in renal transplant recipients with impaired renal allograft function.

## MATERIALS AND METHODS

### Patients

We retrospectively reviewed the records of 11 renal allograft recipients with chronic HCV infection who were treated with the fixed-dose combination of GZR/EBR between December 2016 and April 2017. Renal transplant recipients with impaired renal transplant function (GFR lower than 40 mL/min per 1.73 m<sup>2</sup>) were considered for treatment with a sofosbuvir-free regimen. Our threshold for avoiding a sofosbuvir-based regimen was higher than that recommended by current guidelines (a threshold GFR lower than 30 mL/min per 1.73 m<sup>2</sup>).<sup>3</sup> We aimed to eliminate the risk of DAA treatment interruptions resulting from short-term deterioration of renal transplant function (eg, in case of infection or drug toxicity). One patient received GZR/EBR because of an adequately low renal transplant function level at the screening time point before treatment initiation. The chosen DAA regimen was not changed despite superior renal transplant function at treatment follow-up. Transplant recipients with a history of or evidence of hepatocellular carcinoma, decompensated liver disease, chronic hepatitis B, or human immunodeficiency virus infection, as well as patients with cyclosporine-based immunosuppressive therapy and those with evidence of NS5A/NS3 resistance-associated variants (RAVs), were excluded from the study.

Anti-HCV treatment was undertaken after patients had been thoroughly informed about the adverse effects of therapy and the possible interactions between DAAs and their current immunosuppressive regimens. Clinical, technical, and laboratory data were collected from patients' charts and retrospectively analyzed. The analysis was done in accordance with the Declaration of Helsinki and was approved by the ethics commission of the University Hospital Essen (Ethics approval, 16-6832-BO).

### Antiviral Treatment Regimen and Assessment of Treatment Response

Ten of the 11 patients were treated with GZR (100 mg) and EBR (50 mg) as a fixed-dose combination tablet once daily for 12 weeks. The remaining patient underwent treatment for 16 weeks because his viral load was high at baseline (2.2 E6 log<sub>10</sub> IU/mL) and decreased slowly during treatment.

To evaluate the effectiveness of GZR/EBR, we determined viral load before the initiation of therapy (baseline) and then weekly for the first 4 weeks, at weeks 8 and 12 during treatment, and again 4 weeks and 12 weeks after the end of treatment (EOT). Plasma HCV RNA levels were monitored with the Abbott RealTime HCV Viral Load Assay (Abbott Molecular Inc, Des Plaines, IL; lower limit of detection, 12 IU/mL). Sustained virologic response (SVR) was defined as an undetectable viral load 12 weeks after EOT. Viral relapse was defined as recurrence of a detectable viral load.

For all patients, the NS5A protease domain and the NS3 domain of the virus were sequenced routinely before the initiation of therapy to allow the exclusion of patients with NS5A RAVs, which are associated with resistance to GZR, or NS3 RAVs, which are associated with resistance to EBR. Sequences were analyzed with the resistance prediction algorithm as implemented in the interpretation system geno2pheno[HCV] 0.92 from the Max Planck Institute (<http://hcv.bioinf.mpi-inf.mpg.de>). All patients tested negative for NS5A and NS3 RAVs.

Transient elastography, as measured with the FibroScan 502 (Echosens, Paris, France), was used to determine liver stiffness before treatment (at baseline) and 4 weeks after EOT. Measurements were performed by several experienced operators. At each time point, 10 measurements were obtained and were averaged to create a mean measurement of liver elasticity (in kPa). This measurement served as an estimate of liver fibrosis before and after therapy.

### Immunosuppressive Regimen and Evaluation of Renal Allograft Function

At the time of renal transplant, 5 of the 11 patients underwent induction therapy with antithymocyte globulin (n = 2), basiliximab (n = 2), or daclizumab (n = 1) in addition to a standard immunosuppressive regimen at the time of transplantation. Induction therapy with antithymocyte globulin was used for 2 patients with panel-reactive antibodies higher than 25% at the time of transplantation. Since 2011, our center's policy has been to administer basiliximab (or daclizumab) as induction therapy for all renal transplant patients. The patients' baseline immunosuppressive regimens are shown in Table 1. At the initiation of anti-HCV therapy, 7 patients were treated with a standard immunosuppressive regimen consisting of a low-dose steroid in combination with tacrolimus (TAC) and mycophenolate mofetil (MMF; n = 6) or mycophenolate acid (MPA; n = 1); 1 patient was treated with steroids in combination with azathioprine and TAC; 2 patients were treated with steroids and TAC alone; and 1 patient was treated with steroids plus TAC and everolimus. Therapeutic levels of immunosuppressive medications, such as TAC and everolimus, were monitored routinely. The mean prednisolone dosage for all patients was 4.77 ± 1.35 mg/d. The dosage of MMF was 1000 mg/d (n = 2), 1500 mg/d (n = 2), or 2000 mg/d (n = 2). The dosage of MPA was 180 mg/d (n = 1).

**TABLE 1.****Patient characteristics at baseline**

Demographic characteristics	Values
Age: median (range), y	52 (48–68)
Sex: men/women, n	9/2
Time from renal transplant to HCV therapy: median (range), mo	110 (44–298)
No. previous renal transplants, n	7
Previous biopsy because of proteinuria, n	5
Cause of end-stage renal disease	
Nephronophthisis, n	2
Chronic glomerulonephritis, n	2
Reflux nephropathy, n	1
Alport syndrome, n	1
Other or unknown, n	5
Immunosuppressive regimens	
TAC/azathioprine/everolimus, n	11/1/1
MMF/MPA coadministration, n	7
Steroid coadministration, n	11
Baseline viral characteristics	
HCV genotype:	
1a, n	2
1b, n	8
4, n	1
Viral load ( $\log_{10}$ IU/mL), median (range)	$9.9 E^5$ ( $2.2 E^5$ – $4.6 E^6$ )
Previous anti-HCV treatment	None
Baseline laboratory values; median (range)	
Creatinine, mg/dL	2.35 (1.46–3.65)
eGFR, mL/min per 1.73 m <sup>2</sup>	29 (15–48)
Proteinuria, mg protein/g urine creatinine	761.7 (5–6071)
Albuminuria, mg albumin per g creatinine	508.6 (13.8–4659)
Bilirubin, mg/dL	0.4 (0.2–0.6)
GGT, U/L	55 (32–567)
ALT, U/L	40 (14–100)
AST, U/L	29 (19–85)
AP, U/L	86 (36–116)
Total serum protein, g/dL	7.18 (6.42–7.96)
Albumin, g/dL	4.2 (3.6–4.6)
AFP, IU/mL	2.5 (1.1–7.2)
Hemoglobin, g/dL	13.3 (9.5–15.4)
WBC count, cells/ $\mu$ L	7.57 (3.37–10.9)
Platelet count, cells/nL	226 (129–313)
Baseline technical variable: median (range)	
Fibroscan, kPa	4.9 (2.4–11)

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transpeptidase; HCV, hepatitis C virus; MMF, mycophenolate mofetil; MPA, mycophenolate acid; TAC, tacrolimus; WBC, white blood cell.

Laboratory values associated with liver and renal function and trough levels of immunosuppressants were assessed at baseline, weekly for the first 4 weeks of treatment, and again at treatment weeks (TW) 8 and 12. All measurements were repeated at weeks 4, 12, and 24 after EOT.

The GFR was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.<sup>6</sup> The protein-to-creatinine ratio in spot urine was used as an estimate of the level of proteinuria. Tacrolimus and everolimus levels were measured with immunoassays (Abbott Diagnostics, Lake Forest, IL; Siemens Healthcare Diagnostics Inc., Deerfield IL). All other laboratory values were determined by routine methods.

**Statistical Analysis**

Data are given as medians with ranges or as means with standard deviations (SD). Repeated measurements were analyzed with 1-way analysis of variance and the Friedman test. Differences in clinical variables at baseline and at EOT were analyzed with 2-tailed Wilcoxon matched-pairs tests. Statistical significance was assigned at the *P* level of 0.05 or less. Statistical analyses were performed with GraphPad Prism software, version 6.

**RESULTS****Patient Characteristics**

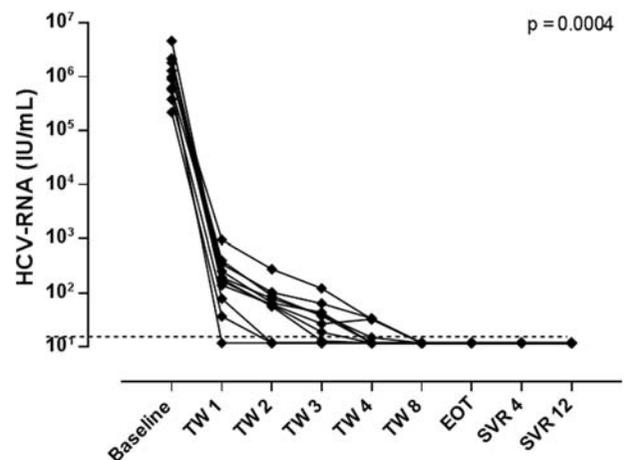
Overall, 10 of the 11 renal allograft recipients with chronic HCV infection and advanced renal transplant dysfunction were treated with the fixed-dose combination of GZR/EBR without RBV once daily for 12 weeks. The 11th patient with HCV GT1a infection was treated with GZR/EBR for 16 weeks because of a high initial viral load. Data from these patients were retrospectively analyzed. Baseline patient characteristics are shown in Table 1.

**Virologic Response**

Eight of our patients were infected with HCV GT1b, 2 were infected with HCV GT1a, and one was infected with HCV GT4. No patients had been previously treated for HCV infection. Pretreatment examination detected no RAVs in any patient. The median time between kidney transplant and the initiation of antiviral treatment was 110 months (range, 44–298 months). We found a median HCV RNA concentration of  $9.9 E^5$  (range,  $2.2 E^5$ – $4.6 E^6$ )  $\log_{10}$  IU/mL at baseline. At TW4, 7 patients (64%) had an undetectable viral load (HCV GT1a, *n* = 2; HCV GT1b, *n* = 5) (Figure 1), but 4 patients exhibited persistent detectable HCV viremia (HCV RNA, 0–33 IU/mL); 3 of these were infected with HCV GT1b and one with HCV GT4. At TW 8, these 4 patients exhibited a virologic response. All patients exhibited an EOT response after 12 weeks (*n* = 10) or 16 weeks (*n* = 1) of treatment, and all 11 patients exhibited SVR at 12 weeks after treatment.

**Safety**

The once-daily combination of GZR/EZR was generally well tolerated by all 11 renal transplant recipients. No serious



**FIGURE 1.** Anti-hepatitis C virus (HCV) ribonucleic acid (RNA) viral load in 11 HCV-positive renal transplant patients before, during, and after treatment with grazoprevir (GZR)/elbasvir (EBR). EOT, end of treatment; SVR, sustained virologic response; TW, treatment weeks.

adverse effects or deaths occurred during treatment. The most common adverse effects were arterial hypertension ( $n = 8$ ), gastrointestinal symptoms ( $n = 7$ ), fatigue ( $n = 6$ ), and headache ( $n = 3$ ), all of which were either mild or moderate in intensity. One patient reported episodes of hyperglycemia, and 1 patient reported myalgia during the first 4 weeks of treatment. No patients discontinued antiviral treatment because of adverse effects.

### Renal Allograft Function

All kidney transplant patients exhibited impaired renal function with a median estimated GFR (eGFR) of 29 mL/min per 1.73 m<sup>2</sup> (range, 15–48 mL/min per 1.73 m<sup>2</sup>) at the beginning of therapy. Renal allograft function did not worsen during therapy with GZR/EBR. All patients exhibited stable GFR rates during the treatment course and thereafter (Figure 2). Median GFR values were 30 mL/min per 1.73 m<sup>2</sup> (range, 13–41 mL/min per 1.73 m<sup>2</sup>) at EOT and 27 mL/min per 1.73 m<sup>2</sup> (range, 5–50 mL/min per 1.73 m<sup>2</sup>) at 12 weeks after EOT (Figure 2A). No significant improvement in renal allograft function was observed during 12 weeks of treatment or during the follow-up period. No episodes of allograft rejection were recorded during antiviral therapy. At follow-up week 4 after EOT, 1 patient experienced allograft failure requiring chronic dialysis (Figure 2B). Allograft failure was not associated with DAA therapy or HCV infection but was related to biopsy-proven progressive diabetic nephropathy in the renal graft because of posttransplant diabetes mellitus; this condition had been diagnosed before the initiation of HCV therapy. No significant changes in the median levels of proteinuria were detected in allograft recipients before or after anti-HCV therapy (Figure 2C). At the initiation of DAA therapy, 6 of 11 patients exhibited proteinuria of more than 500 mg/g urine creatinine. Three patients experienced persistent proteinuria caused by

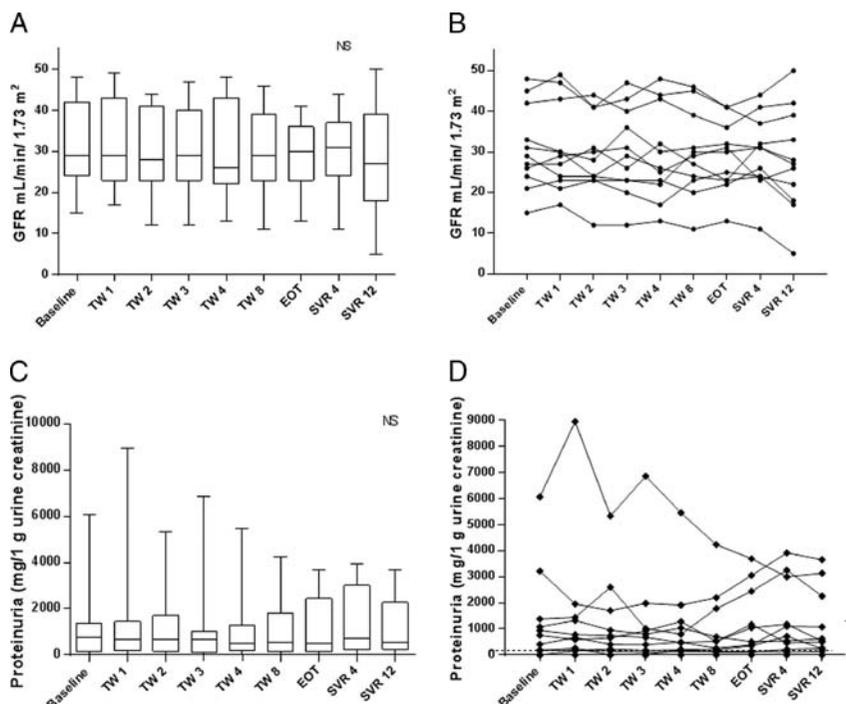
biopsy-proven chronic ABMR, which was treated with plasmapheresis and subsequent administration of immunoglobulin before the initiation of DAA therapy. One patient exhibited histologic signs of chronic transplant pyelonephritis with infiltration of granulocytes, and 1 patient had diabetic nephropathy. One patient had stable proteinuria at a level of 1 g/g urine creatinine; this condition was not histologically evaluated because of stable renal allograft function, lack of donor-specific HLA antibodies, and the patient's decision. Individual proteinuria values remained mostly stable during and after DAA treatment, except for 1 patient with previous biopsy-proven chronic antibody-mediated rejection (Figure 2D).

### Immunosuppressive Therapy

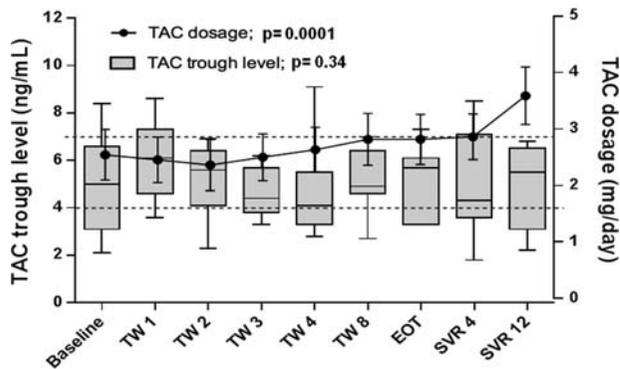
The immunosuppressive regimens given at the initiation of antiviral treatment are displayed in Table 1. All patients were treated with a TAC-based regimen. After 4 weeks of therapy, trough levels of TAC had declined moderately, requiring an adjustment of the daily dosage (Figure 3). Nine (82%) patients required dose adjustments of TAC for maintenance of adequate trough levels: mean TAC dosage/concentration ratio was 0.58 mg/ng per day (range, 0.12–1.52 mg/ng per day) at baseline; 0.56 mg/ng per day (0.21–0.97 mg/ng per day) at EOT; and 0.86 mg/ng per day (0.23–1.82 mg/ng per day) 12 weeks after EOT. Everolimus was combined with TAC for 1 patient. For this patient, the trough level of everolimus had decreased slightly at TW4, requiring minor dosage modifications ( $n = 1$ ; data not shown).

### Liver Function Parameters

All renal allograft recipients exhibited an improvement in liver function during the course of GZR/EBR therapy. The activity of alanine aminotransferase (ALT) and aspartate

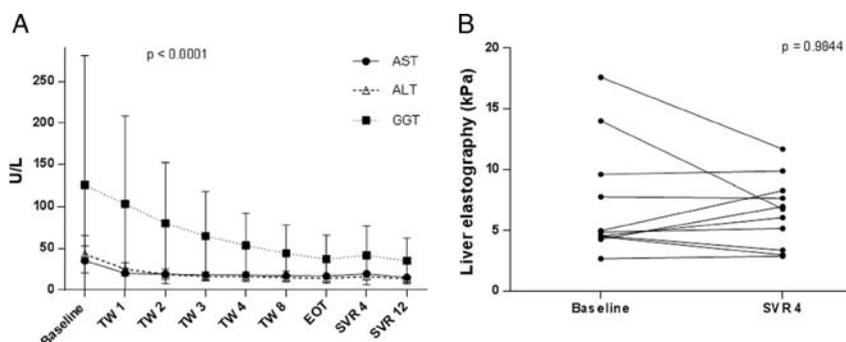


**FIGURE 2.** Renal allograft function and proteinuria in 11 renal transplant patients with advanced Chronic Kidney Disease (CKD) before, during, and after treatment with grazoprevir (GZR)/elbasvir (EBR). A, Boxplots of median glomerular filtration rate (GFR) values at each time point. B, Individual GFR rates at each time point. C, Boxplots of median proteinuria values at each time point. D, Individual proteinuria levels at each time point. EOT, end of treatment; SVR, sustained virologic response; TW, treatment weeks.



**FIGURE 3.** Tacrolimus (TAC) trough levels and dosages for 11 renal transplant patients before, during, and after treatment with grazoprevir (GZR)/elbasvir (EBR). TAC trough levels are presented as boxplots, and TAC dosages are presented as means with standard error of the mean (SEM). EOT, end of treatment; SVR, sustained virologic response; TW, treatment weeks.

aminotransferase (AST) decreased significantly from baseline levels as EOT approached ( $P < .0001$ ; Figure 4A). The initially elevated activity of gamma-glutamyl transpeptidase (GGT) also normalized quickly, by 8 weeks after the initiation of therapy ( $P < .0001$ ; Figure 3A). The activity of transaminases and GGT was stable within normal ranges at 12 weeks after EOT. AST activity decreased from the baseline median level of 29 U/L (range, 19–85 U/L) to 18 U/L (range, 12–20 U/L) at EOT and to 14 U/L (range, 11–21 U/L) at 12 weeks after EOT ( $P < .0001$ ). ALT activity decreased from the baseline median level of 40 U/L (range, 14–100 U/L) to 13 U/L (range, 9–20 U/L) at EOT and to 15 U/L (range, 9–20 U/L) at 12 weeks after EOT ( $P < .0001$ ). Similarly, GGT activity decreased from a median of 55 U/L (range, 32–567 U/L) at baseline to 26 U/L (range, 18–117 U/L) at EOT; it remained steady at 26 U/L (range, 12–104 U/L) at 12 weeks after EOT ( $P < .0001$ ). However, there were no statistically significant differences between pretreatment and posttreatment serum bilirubin levels, international normalized ratios, and alkaline phosphatase activity (data not shown). Although liver stiffness showed a trend toward improvement in 2 patients with pretreatment values higher than 10 kPa, no significant changes in liver stiffness were found in patients with normal liver elasticity levels at the initiation of treatment (Figure 4B).



**FIGURE 4.** Parameters related to liver function and fibrosis in 11 renal transplant patients before, during, and after treatment with grazoprevir (GZR)/elbasvir (EBR). Data are presented as means with standard deviation (SD). A, Activity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (GGT). B, Liver elastography as determined by Fibroscan at baseline and after a follow-up period of 4 weeks after end of treatment (EOT). Data are presented as medians with interquartile range. SVR, sustained virologic response; TW, treatment weeks.

## DISCUSSION

A cohort of 11 renal allograft recipients with chronic HCV GT1a, GT1b, or GT4 infection was treated with GZR/EBR. None of the patients had been previously treated for HCV. All patients exhibited a SVR at 12 weeks after EOT (SVR12) with no serious adverse effects, including acute renal dysfunction and rejection. After the initiation of DAA therapy, TAC trough levels decreased, but these decreases could be corrected by a moderate dose adjustment. Despite a markedly impaired GFR at the initiation of GZR/EBR treatment, renal allograft function remained stable during and after treatment, except for 1 patient with progressive diabetic nephropathy of the transplanted organ. Hepatic inflammation, characterized by elevated liver enzyme activity, was substantially reduced after treatment. Liver elastography showed a trend toward improvement in those patients with baseline levels indicating impairment in liver function. Overall, these results indicate that treatment with GZR/EBR is safe and effective for renal transplant recipients with impaired renal allograft function (GFR lower than 30 mL/min per 1.73 m<sup>2</sup>).

GZR is an NS3/4A protease inhibitor, whereas EBR is an NS5a inhibitor. The main route of elimination is the biliary tract (>90%); renal elimination is extremely low (<1% in urine). Treatment with GZR/EBR has been shown to be safe and effective for patients with chronic HCV GT1 infection and advanced chronic renal kidney disease, as well as for dialysis patients; this RBV-free combination therapy achieves SVR12 for 94% of patients.<sup>7</sup> To our knowledge, we are the first to present the results achieved by using this combination therapy to treat renal transplant recipients with impaired graft function (GFR lower than 30 mL/min per 1.73 m<sup>2</sup>).

New treatment options for renal transplant recipients require careful evaluation with regard to DDIs with immunosuppressants. Calcineurin inhibitors (TAC and cyclosporine) and mechanistic target of rapamycin inhibitors (everolimus, sirolimus) are substrates of cytochrome P450. For this reason, they exhibit clinically relevant interactions with many DAAs, such as ombitasvir and ritonavir.<sup>8</sup> Recently, various sofosbuvir-based regimens have been used to treat renal transplant recipients with chronic HCV infection; these regimens should theoretically not interact with cytochrome P450 activity and have been shown to be effective in eliminating HCV virus from renal transplant recipients.<sup>9–11</sup> A moderate but relevant decrease in calcineurin inhibitor levels has been

observed with several sofosbuvir-based regimens.<sup>10,11</sup> Our cohort of 11 patients was treated with a TAC-based immunosuppressive regimen; cyclosporine comedication was not appropriate because it leads to a threefold increase in GZR-levels.<sup>4,12</sup> We observed only a moderate decrease in trough levels of TAC, requiring adjustments in the TAC dosage for 9 of the 11 patients treated with GZR/EBR. A recent publication reported that 3 liver transplant recipients who required dialysis were treated with GZR/EBR and required frequent adjustments of the TAC dosage during HCV treatment.<sup>5</sup>

In our cohort, although the mean GFR was 29 mL/min per 1.73 m<sup>2</sup>, renal allograft function remained stable during treatment with GZR/EBR. One patient with advanced diabetic glomerulopathy in the kidney graft exhibited end-stage renal disease after EOT; this adverse effect was most likely not related to DAA treatment. A study by Roth and colleagues involved 224 patients with advanced renal disease (CKD stage 4 to 5) who did not undergo transplant; 173 were undergoing dialysis at the initiation of treatment with GZR/EBR. No statistically significant improvement or deterioration in renal function was observed between the immediate HCV treatment group (n = 111) and the delayed HCV treatment group (n = 113).<sup>7</sup>

Proteinuria at a level higher than .5 g/g urine creatinine occurs quite frequently, in more than 50% of all renal transplant patients before the initiation of HCV treatment. We observed no significant changes in proteinuria levels during or after treatment. Our findings are in line with those from a nontransplant cohort with CKD stage 4 or 5.<sup>7</sup>

Adverse effects were mild to moderate and included gastrointestinal symptoms, fatigue, headache, and arterial hypertension. These effects are often described in association with protease inhibitor treatment.<sup>7,13</sup> A worsening of arterial hypertension was observed in 8 of our 11 patients. Because most of our patients were taking antihypertensive medications, a potential DDI may have caused this phenomenon.

Substantial evidence indicates that chronic HCV infection among renal allograft recipients is associated with a higher risk of renal impairment and graft loss and with higher mortality rates.<sup>14-16</sup> For renal allograft recipients, HCV has been implicated in the pathogenesis of glomerular diseases and in the occurrence of new-onset diabetes after transplantation, conditions that may lead to cardiovascular disease and malignancy.<sup>17-21</sup> This incidence supposes that chronic HCV infection requires consequent treatment, the more so because chronic HCV infection is no longer an important challenge for renal transplant recipients.<sup>16,22-24</sup> We and others have shown that sofosbuvir-based regimens are highly effective in treating HCV infection in renal transplant recipients with a stable GFR higher than 30 to 40 mL/min per 1.73 m<sup>2</sup>.<sup>9-11</sup> Although impaired graft function in renal transplant patients with chronic HCV infection has so far minimized treatment options with DAAs, a large randomized cohort study recently demonstrated the efficacy and safety of combination therapy with GZR/EBR for renal patients with CKD stage 5 with or without dialysis.<sup>6</sup> Here we report that HCV treatment with GZR/EBR is an effective and safe option for renal transplant recipients with chronic HCV infection and impaired renal allograft function. This new treatment option for HCV also changes the paradigm for using HCV-positive donor organs. Patients on the transplant waiting list whose liver function is not substantially impaired can be given an

HCV-infected allograft and can begin antiviral treatment early after transplant, with predictable benefits similar to those reported for patients with hepatitis B infection.<sup>25-27</sup> A recent study reported the successful use of GZR/EBR as pretransplant prophylaxis for noninfected recipients of a kidney transplant from an HCV-infected donor.<sup>28</sup>

The available data are limited and do not yet indicate the ideal timing of HCV treatment after renal transplant. Curing HCV earlier in the posttransplant course may theoretically offer benefits such as lower rates of HCV-associated nephropathy, new-onset diabetes, and cryoglobulin-related and liver-related complications. Of course, these benefits must be balanced with the risk of acute kidney injury early after renal transplant because of the potential for DDIs between DAAs and immunosuppressive agents. In any case, HCV treatment before and after kidney transplant is no longer an obstacle.

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## **Treatment With Grazoprevir/Elbasvir for Renal Transplant Recipients With Chronic Hepatitis C Virus Infection and Impaired Allograft Function**

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