Grazoprevir plus elbasvir in HCV genotype-1 or -4 infected patients with stage 4/5 severe chronic kidney disease is safe and effective

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Patients with advanced chronic kidney disease who receive direct-acting antiviral drugs require special consideration regarding comorbid conditions. Here we assessed the efficacy and safety of grazoprevir plus elbasvir in 93 patients infected with HCV genotype 1 or 4 and with advanced chronic kidney disease in a non-randomized, multicenter, nationwide observational survey. Twenty patients with HCV genotype 1a, 51 patients with 1b, four unclassified genotype 1, 17 with genotype 4 and one with genotype 6 received grazoprevir plus elbasvir (100/50 mg) once daily. All patients had severe chronic kidney disease with 70 patients stage G5, including patients on hemodialysis (74.2%), and 23 were stage G4 chronic kidney disease. Severe liver disease (Metavir F3/F4) was found in 33 patients. A sustained virologic response 12 weeks after the end of therapy was achieved in 87 of 90 patients. Two patients had a virologic breakthrough and one had a relapse after treatment withdrawal. Most patients received many concomitant medications (mean 7.7) related to comorbid conditions. Serious adverse events occurred in six patients, including three deaths while on grazoprevir plus elbasvir, not related to this therapy. Thus, once-daily grazoprevir plus elbasvir was highly effective with a low rate of adverse events in this advanced chronic kidney disease difficult-to-treat population with an HCV genotype 1 or 4 infection.

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The prevalence of hepatitis C virus (HCV) infection in patients with end-stage renal disease (ESRD), despite its prevalence declining over time, remains 4 times greater in dialysis patients and kidney-transplant recipients than in the general population.[1–4] In the general population, apart from its impact on the liver, chronic HCV infection is associated with increased global mortality related to higher rates of diabetes, neurologic stroke, and cardiovascular disease. In addition, HCV infection increases the risk of chronic kidney disease (CKD), leading to ESRD.[5] After renal transplantation, HCV infection is an independent factor for global mortality and the loss of the kidney graft.[6] This worse prognosis in HCV-infected kidney recipients is usually thought to be caused in part by a more rapid progression of liver fibrosis and an increased risk of *de novo* transplant glomerulopathy.[7,8]

Currently, direct-acting antiviral drugs (DAAs) are the gold standard for treating HCV infection.[9] There are numerous types of DAAs, and the combination of at least 2 different classes results in a high sustained virologic response, as defined by an undetectable HCV RNA 12 weeks after the end of therapy (SVR12). Sofosbuvir was the first pan-genotypic DAA to become available. A second wave of DAAs that are active against HCV genotypes 1, 2, 3, 4, 5, and 6 were subsequently approved. A combination of these drugs, with or without ribavirin, has been shown to be effective and well tolerated in treatment-naïve

and treatment-experienced patients with HCV infection. Indeed, >90% of HCV patients can be cured of the infection, and an SVR is generally associated with resolution of liver fibrosis in patients without cirrhosis.[9] Because sofosbuvir is primarily eliminated by the kidney,[10] its use is not recommended for patients with ESRD, including patients with an estimated glomerular filtration rate (eGFR) <30 ml/min per 1.73 m^2 or those receiving hemodialysis. Consequently, the safety and efficacy of sofosbuvir-containing regimens have not been clearly established in such patients. In addition, therapy with DAAs given to CKD patients requires special consideration regarding comorbid conditions and drug-to-drug interactions.[10–12] Phase 2 and 3 trials using grazoprevir (GZR), an NS3/4A protease inhibitor, and elbasvir (EBR), an NS5A protein inhibitor of HCV, have shown very good results against HCV genotype 1 and 4 infections.[13,14] Less than 1% of GZR+EBR is renally excreted; thus, dose adjustments of GZR+EBR are not needed for patients with nondialysis-dependent stage 4/5 CKD or those who are dialysis dependent. C-Surfer[15] was the first randomized, placebo-controlled phase 3 study to evaluate an all-oral, ribavirin-free regimen in HCV genotype 1–infected patients, with stage 4 or 5 advanced CKD, including subjects on hemodialysis. Once-daily GZR+EBR was highly effective, with a low rate of adverse events in patients with advanced CKD and a HCV genotype 1 infection. Taking into account the results of the C-Surfer study, GZR+EBR is a good therapy option for this specific population.

In 2015, the French National Agency for Medicine and Health-Product Safety granted nominative temporary authorization (ATUn) for the use of GZR+EBR, which is an early-access program that gives patients access to a medication before it is authorized for marketing. Patients were mainly CKD stage 4/5, infected with HCV genotype 1 or 4, sometimes with a history of kidney or liver transplantation or on a transplantation list, were treatment-naïve or experienced, regardless of fibrosis stage or comorbid conditions. Most of these patients had been excluded from phase 2 or 3 trials.

The aims of this multicenter cohort study were to report, in real-life clinical practice, the efficacy and safety of GZR + EBR-based therapy given to HCV-infected patients with advanced CKD and differing clinical profiles.

RESULTS

Characteristics of patients at baseline

As shown in Figure 1, 93 patients with CKD were included in the study. They were enrolled at 28 centers, and 90 patients reached week 12 of the follow-up after GZR + EBR withdrawal. Three patients died while receiving GZR + EBR; thus, SVR12 was not assessed. The baseline demographic and disease characteristics are shown in Table 1. Most patients were on hemodialysis (69/93, 74.2%). All patients had severe CKD: 70 (75.3%) were stage G5 and 23 (24.7%) were stage G4. The duration of hemodialysis before GZR + EBR treatment was 27.5 ± 3.5 months. Previous anti-HCV treatment with pegylated interferon + ribavirin failed in 37 patients (39.8%). Most patients were HCV genotype 1b (54.8%); the prevalence of HCV genotype 1a (21.5%) or genotype 4 (18.3%) was substantial. At baseline, liver fibrosis was mild in 53 patients (57.0%), and severe liver disease (METAVIR F3/F4) was observed in 33 patients (35.5%); 19 patients (20.4%) were METAVIR F3. Fourteen patients (15.1%) had compensated cirrhosis. Most of the patients (76.3%) received GZR + EBR for 12 weeks, 16.1% for 16 weeks, and only 1 patient for 24 weeks (Table 1). This extended duration of antiviral therapy was for patients with HCV genotype 1a infection or those with cirrhosis. Six patients (6.5%) were treated for <12 weeks due to adverse events or because the patient requested that treatment was stopped. Only 3 patients (3.2%) received GZR + EBR in association with ribavirin: at a low dose of 200 mg/day for 2 patients, and 600 mg/d for 1 patient.

Viral efficacy

Of the 90 patients who received GZR + EBR and completed the 12-week follow-up after treatment withdrawal, a virologic response at the end of antiviral therapy was observed in

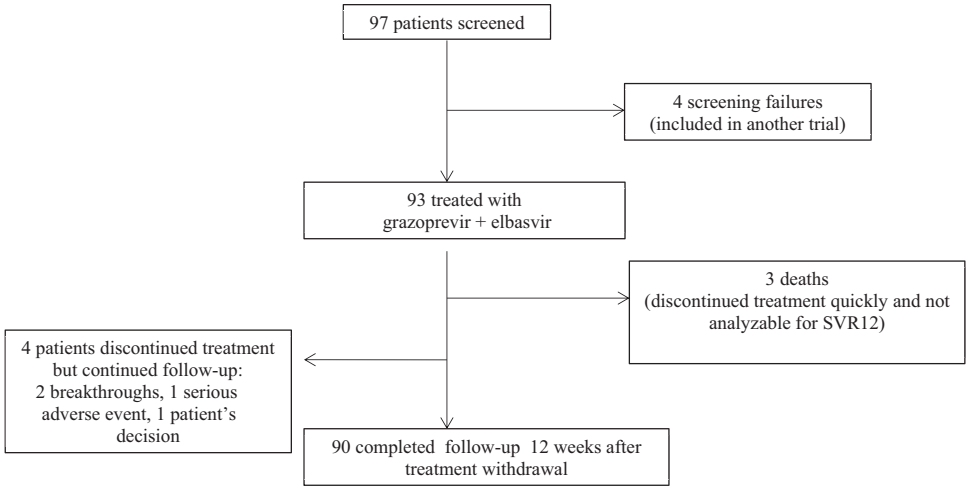

Figure 1 | Flowchart. SVR12, sustained virologic response at week 12 of follow-up after grazoprevir + elbasvir withdrawal.