ORIGINAL ARTICLE

DAA-based antiviral treatment of patients with chronic hepatitis C in the pre- and postkidney transplantation setting

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SUMMARY

DAA-based regimens for chronic hepatitis C infection encourage treatment of "difficult-to-treat" cohorts. This study investigated efficacy and safety of DAA-based regimens in HCV patients on dialysis or postkidney or liver/kidney transplantation. Twenty-five patients treated with DAA combinations were evaluated: 10 were on dialysis (eight: hemodialysis, two: peritoneal dialysis), eight were kidney transplant recipients, and seven were liver/kidney transplant recipients. Except for one patient treated with daclatasvir ([DCV]/60 mg/QD)/simeprevir ([SMV]/150 mg/QD), the others received sofosbuvir-based regimens ([SOF];400 mg/QD) combined with SMV:eight, DCV:13 or either ledipasvir ([LDV]90 mg/QD), ribavirin ([RBV];weight based) or pegylated interferon/RBV. HCV-RNA was determined by Abbott RealTime (LLOQ]:12 IU/ml) or Roche AmpliPrep/COBAS TaqMan assay (LLOQ:15 IU/ml); treatment response evaluated every 4 weeks, at the end of treatment, and 4 and 12 weeks thereafter. Twenty-four (96%) patients achieved SVR 12/24 (ITT-analysis). Mean treatment duration was 15.1 ± 5.1 weeks (±SD), and two patients terminated prematurely – both reached SVR12. Six patients were hospitalized due to complications of underlying disease. One patient achieved SVR24 but was re-infected (week 27). Kidney function remained stable; serum creatinine increased in only one patient – SOF was reduced to 400 mg/48 h. Treatment with DAA combinations in renally impaired HCV patients is highly effective and well tolerated. These findings call for further controlled trials and data from real-life cohorts.

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Key words
chronic kidney disease (CKD), dialysis, direct-acting antivirals (DAA), end-stage renal disease (ESRD), IFN-free, renal transplantation

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Introduction

The availability of interferon-free and all-oral direct-acting antiviral (DAA)-based treatment regimens allows to treat "difficult-to-cure" patients with chronic hepatitis C virus infection (HCV [1,2]) including those with chronic kidney disease (CKD). Ongoing studies in HCV patients with chronic kidney disease (CKD – stages IV

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and V) [3,4] provide only limited data in patients with end-stage renal disease (ESRD) on dialysis (CKD V) in the need of transplantation or renal transplant recipients. Only one study treating CKD IV–V patients with an experimental drug combination has been published [5], and few data on the treatment of patients after renal transplantation are available so far [6,7].

The association of chronic kidney disease (CKD) and HCV infection is well established, most frequent being type I membrano-proliferative glomerulonephritis, usually in the context of type II mixed cryoglobulinemia [8] – bearing risk to develop ESRD [9–13]. Nevertheless, the majority of renal transplant recipients acquired HCV infection during hemodialysis (HD); hence, prevalence of anti-HCV antibodies detected in these patients, assessed by ELISA, varied between 3% and 10% in developed and 15% and 75% in developing countries. Estimated prevalence in HD patients was shown to decrease due to the reinforcement of hygienic precautions and/or isolation strategies in developed countries to 2–8% [14]. HCV infection in renal transplant recipients increases the risk of graft loss, cirrhosis, hepatocellular carcinoma, and death [13,15–19]. Therefore, "Kidney Disease: Improving Global Outcomes" (KDIGO) recommended to evaluate all CKD patients with HCV for possible antiviral therapy [19].

Up to now, treatment options in patients with impaired renal function were limited to (pegylated) interferon combined with (low-dose) ribavirin (PR), but side effect within this treatment frequently required premature discontinuation and resulted in high dropout rates and high treatment-related mortality; hence, only few HCV-infected ESRD patients requiring hemodialysis were treated [9].

The Dialysis Outcomes and Practice Patterns Study (DOPPS) reported 4735 (9.5%) of 49 762 hemodialysis patients being HCV positive, but only about 1% received antiviral treatment [20]. The hazard ratio for adjusted mortality, comparing treated versus untreated patients, was 0.47, indicating that treatment of HCV infection is recommended for patients undergoing dialysis [14]. In renal transplant patients, interferon-based treatment is contraindicated as rejection episodes occurred regardless of the dose of interferon-alpha dosing and immunosuppressive regimen [14,21,22]. In addition, ribavirin decreases relapse rates after interferon therapy [23] but is poorly tolerated in patients with ESRD due to increased toxicity when creatinine clearance is below 50 ml/min [9].

Currently, little is known of the tolerability of DAA-based regimens in patients with impaired renal function. As SOF and its metabolites (GS-331007) are renally excreted [24], package insert does not recommend full dose of SOF regimens in patients with eGFR <30 ml/1.73 m^2/min [23,24,25,26]. However, these limitations are not based on clinical data up to now. International societies (EASL [5]; AASLD [27]) recommend simeprevir, daclatasvir, and the 2D/3D combination (ritonavir-boosted paritaprevir/ombitasvir ± dasabuvir) for treatment of patients with severe renal disease, as these components are metabolized mainly by the liver.

This real-life study aimed to evaluate efficacy and safety data of DAA-based regimens in ESRD patients on hemodialysis, after kidney or simultaneous liver/kidney transplantation as part of the AURIC trial (NCT02628717).

Patients and methods

Patients

All 25 patients described in this analysis were treated as soon as the various medications became available. Data were submitted to a central database continuously; evaluation was performed retrospectively. Within this cohort, 10 patients were on dialysis (hemodialysis [HD]: $N = 8$; peritoneal dialysis [PD]: $N = 2$); the transplant population ($N = 15$) consisted of kidney ([NTX: renal transplantation]; $N = 8$) or liver/kidney ([NTX/OLT: orthotopic liver transplantation]; $N = 7$) recipients. The post-transplant population included 6 patients with renal impairment (chronic kidney disease [CKD] III-IV: $N = 5$ [GFR 15–59 ml/1.73 m^2/min]; CKD V: $N = 1$ [GFR <15 ml/1.73 m^2/min]). Thus, the study cohort included a total of 16 (64%) renally impaired patients. Five patients were on waiting list for transplantation or re-transplantation before starting antiviral treatment: three for kidney transplantation; one for simultaneous liver/kidney transplantation; one NTX patient for orthotopic liver transplantation (OLT). Ten (40%) patients were treatment-experienced, 12 (48%) patients had cirrhosis (diagnosed by either liver biopsy or determination of liver stiffness [FibroScan® [Touch 5.02; Echosens; Paris; France]; cutoff for cirrhosis: 12.5 kPa]). The demographics of evaluated patients are given in Table 1. All medications were prescribed and covered by the Austrian Public Social Insurance System.

The decision for appropriate treatment regimen and duration was made by the physician's discretion. Except for one patient receiving 60 mg/QD daclatasvir (DCV) combined with 150 mg/QD simeprevir (SMV), all patients received 400 mg/QD sofosbuvir (SOF)

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Table 1. Patients characteristics.

Parameter	Total	Dialysis	Post-NTX	Post-NTX/OLT
Complete cohort	25	10	8	7
Male	23			
Age, years	54.5 ± 11.3	50.6 ± 10.9	56.3 ± 11.1	57.6 ± 11.2
Range	31–72	31–69	34–72	34–70
DAA-based regimens				
SOF/PR	1	1		
SOF/LDV	1		1	
SOF/SMV	8	2	3	3
SOF/DCV	13	4	5	4
SOF/RBV	1	1		
DCV/SMV	1		1	
Treatment-experienced	10	4	2	4
(peg)IFN ± RBV	9	4	1	4
PI-triple	1	0	1	0
HCV genotype				
1a	4	2	1	1
1b	12	4	5	3
3a	4	2	0	2
4a/c/d	2	1	1	0
4h	1	0	0	1
4: not specified	1	1	0	0
1b/3a	1	0	1	0
Cirrhosis	12	4	3	5
Compensated (CPS:4)	6	1	0	5
Decompensated (CPS:S/C)	6	3	3	0
HCV RNA IU/ml BL – $\log^{10}$	6.0 ± 0.61	6.1 ± 0.8	5.8 ± 0.5	6.0 ± 0.6
logDrop – week 4	5.3 ± 0.9	5.2 ± 1.0	5.2 ± 1.0	5.4 ± 0.8

NTX, renal transplantation; OLT, orthotopic liver transplantation; DAA, direct-acting antivirals; SOF, sofosbuvir; PR, (pegylated) IFN/ribavirin; RBV, ribavirin; LDV, ledipasvir; SMV, simeprevir; DCV, daclatasvir; GT, genotype; logDrop, reduction in HCV-RNA IU/ml ($\log^{10}$).

Statistics: continuous variables reported as mean ± SD or median (interquartile range), categorical variables as number. Student's *t*-test was used for group comparison of continuous variables as applicable; otherwise, Mann–Whitney *U*-test was applied.

combined with either SMV in eight patients, DCV in 13 patients and in each one with ledipasvir ([LDV]; 90 mg/QD), ribavirin ([RBV]) or pegylated interferon-alpha/RBV ([PR]; 180 μg/week-200 mg/QD).

Planned treatment duration was 12 weeks in 19 patients (HD: 7; NTX: 6; NTX/OLT: 6; SOF/PR: 1; SOF/LDV: 1; SOF/SMV: 8; and SOF/DCV: 8) and 24 weeks in the remaining ones (HD: 3; NTX: 2; NTX/OLT: 1; SOF/RBV: 1; SMV/DCV: 1; SOF/DCV: 4). Planned TX duration of 12 weeks had to be prolonged in three patients (SOF/PR: 1 [12–16]; SOF/SMV: 2 [12 to 16 or 19 weeks, respectively]), and no prolongation was observed for planned 24-week TX duration. Two patients terminated treatment prematurely (week: 8 [planned 12] and 19 [planned 24]). Therapy mode did not differ, whether patients were on dialysis (HD or PD) or after transplant (post-NTX or post-NTX/OLT) and given QD. Two patients received RBV-including regimens; both were on dialysis. The patient treated with SOF/PR received 200 mg RBV QD, and patient treated with SOF/RBV was dosed with 400 mg RBV BID according to HCV genotype (3a). This retrospective analysis was approved by the local ethics committee of the Medical University of Vienna (ECS 1413/2015).

Virological testing

HCV-RNA quantification was performed either with Abbott Real*Time* HCV ([ART], lower limit of quantification [LLOQ]: 12 IU/ml) or Roche COBAS AmpliPrep/COBAS TaqMan assay (LLOQ:15 IU/ml); HCV genotypes were determined using the VERSANT HCV Genotype [GT] 2.0 Assay (LiPA; Siemens Medical Solutions Diagnostics, Tarrytown, NY, USA). All assays were performed according to manufacturer's instructions. On-treatment response was defined as target not

detected (TnD) or lower limit of quantification [LLOQ] (either <12 or <15 IU/ml) evaluated at weeks 2, 4, 8, 12, and 24, respectively; sustained virological response (SVR12/24) was defined as HCV-RNA negativity twelve and 24 weeks after treatment cessation as established.

Statistical methods

Database management and statistical analysis were performed using commercially available software systems (Microsoft Office Excel 2010; Microsoft Corp., Redmond, WA, USA; SPSS 2012 for Mac; Version 20, SPSS Inc., Chicago, IL, USA). Continuous variables are expressed either as mean ± standard deviation (SD) for Gaussian distributions or median (range; 95% CI) for non-Gaussian distributions. Kolmogorov–Smirnov test was applied to determine whether continuous variables were normally distributed. Wilcoxon–Mann–Whitney *U*-test or Student's *t*-test, as appropriate, was used to analyze variables; categorical variables are given as absolute and relative (in percent) frequencies. Group comparisons of categorical variables were computed by Fisher's exact or chi-squared (χ^2) test. All statistical procedures were performed two-sided, and a *P-value* ≤ 0.05 was considered to be statistically significant.

Results

Efficacy

Twenty-four of 25 (96%) of the patients achieved sustained virological response (SVR) after 12 and 24 weeks of treatment free follow-up. One patient relapsed; one patient experienced re-infection; one hemodialysis patient underwent simultaneous liver/kidney transplantation 4 weeks after EoT (naïve, GT3a; CPS:*C*; SOF/RBV planned for 24 weeks; see above), but HCV-RNA relapse was observed at week 12 after EoT; and another HD patient achieved SVR12 as well as SVR24, but at week 27, HCV-RNA was detected again – the patient was known to formerly had IVDA, suggesting re-infection as the most likely cause of late relapse. Unfortunately, the patient did not show up for further controls and HCV genotype retesting was not possible yet.

On-treatment response was slower in HD patients; 5 of 10 (50%) HD patients had detectable HCV-RNA at week 4, compared with 1 of 8 (13%) or 1 of 7 (14%) in the NTX or NTX/OLT group, respectively (Fig. 1). Mean time to first TnD was 7.4 ± 4.5 weeks ([mean ± SD]; IQR range: 2–20; 20 weeks until first TnD was observed in a naïve, cirrhotic GT3a patient on hemodialysis]).

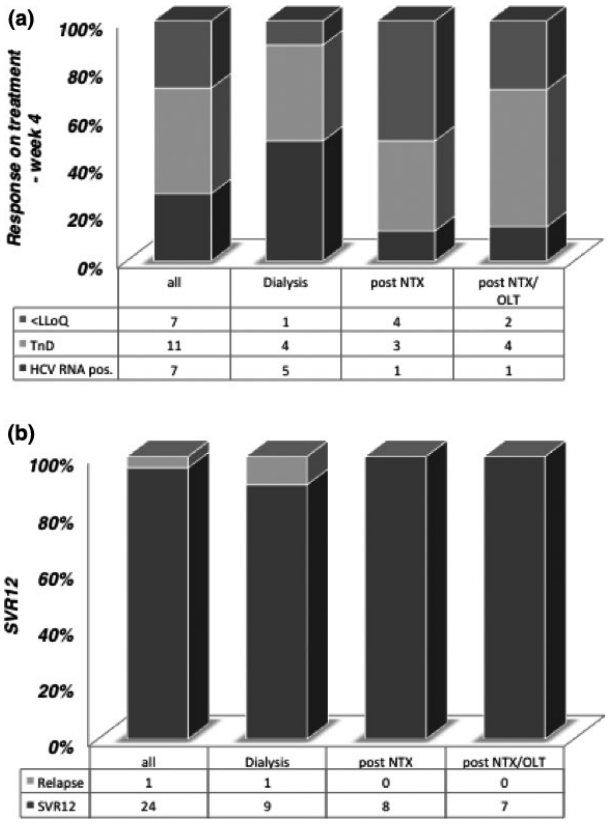

Figure 1 Treatment response at week4 (a) and sustained virological response rates at week12 – intention to treat analysis (b). (a) NTX, renal transplantation; OLT, orthotopic liver transplantation; LLoQ, lower limit of quantification; TnD, target not detected; pos., HCV-RNA positive. (b) NTX, renal transplantation; OLT, orthotopic liver transplantation; SVR12, sustained virological response 12 weeks after end of treatment; Relapse, HCV-RNA detectability following HCV-RNA negativity at EoT; variables reported as proportion of patients.

Fifteen patients were treated for 12 weeks. Treatment was extended for up to 24 weeks because of slow virological response in eight patients (dialysis: $N = 5$; post-NTX: $N = 1$; post-NTX/OLT: $N = 2$), in 2 to 16 weeks (SOF/PR and SOF/SMV, respectively), in one to 19 weeks (with a switch to SOF/DCV after week 11), and in 5 to 24 weeks (SOF/DCV: $N = 3$; DCV/SMV: $N = 1$; SOF/RBV: $N = 1$). Two patients terminated therapy prematurely; one at week 8 (nonadherence), the other at week 19 (OLT), respectively; both achieved SVR12.

Change in renal and hepatic function

In the NTX cohort as well as the NTX/OLT cohort (including six with renal impairment CKD III-V), parameters of kidney function (serum creatinine and eGFR [Cockcroft Gault formula]) were assessed to be entirely

stable undergoing treatment with full-dose SOF-based regimens (Table S2).

In cirrhotic patients, serum albumin levels as well as APRI score and MELD score improved significantly from BL to SVR12 (Albumin [g/l]: 35.6 ± 5.5 vs. 41.0 ± 8.5; [0.05]; APRI: 2.7 ± 2.2 vs. 0.8 ± 1.5 [P = 0.03]; MELD: 15.8 ± 10.5 vs. 11.9 ± 8.9 [P = 0.002]; Table 2). Liver enzymes (aspartate [AST] and alanine [ALT] amino transferase levels) ameliorated in the complete cohort significantly after successful antiviral treatment. Significances (P-values) are outlined in Table S1.

Safety

Six (24%) patients experienced severe adverse events (SAE) requiring hospitalization during treatment.

Severe adverse events

One HD patient, re-listed for NTX due to graft failure, suffered from renal anemia (Hb: 9.2 mg/dl) as well as low WBC (2.52 G/l) before antiviral treatment initiation (SOF/SMV). WBC dropped to 2.13 G/l at week 7 as well as platelet-count dropped from BL 160 G/l to 118 G/l at week 8. Thus, SOF was reduced to 400 mg every other day and SMV switched to DCV. Subsequently, the patient became septic; the origin of infection was due to failed renal graft, which was removed at week 9. In retrospective view, the SAE was unrelated to antiviral therapy.

Another HD patient with graft failure after OLT was referred for evaluation for combined liver/kidney transplantation. At the start of antiviral treatment with SOF/DCV, patient's MELD score was 34. At treatment week 4, the patient was hospitalized because of overt HE as well as therapy-refractory ascites. On-treatment response was excellent (HCV-RNA negative; log-drop till week 4: 5.51 IU/ml). During this admission, small cell lung cancer was diagnosed and as a consequence evaluation procedures for re-OLT suspended. Antiviral therapy was terminated at week 8 (nonadherence), but the patient achieved SVR12 and SVR24.

One peritoneal dialysis patient was hospitalized for recurring peritonitis at treatment week 6 on SOF/DCV. He was admitted for acute peritonitis but recovered on antibiotic treatment. Antiviral therapy was continued for a total of 12 weeks; the patients achieved SVR12 and SVR24. Within the follow-up period (week 13 after EoT), another episode of peritonitis occurred.

In another HD patient, suffering from cirrhosis due to HCV recurrence after OLT, spleen artery embolization was performed at week 9 for severe thrombocytopenia and intractable rectal bleeding despite previous TIPS implantation. Formation of splenic abscess necessitated emergency splenectomy at week 19. Subsequently, the patient developed refractory ascites, requiring TIPS (transjugular intrahepatic portosystemic shunt) revision at week 23. Treatment was continued, and the patient achieved SVR12 and SVR24.

Another HD patient was admitted for pneumonia at treatment week 4 (SOF/RBV) and improved on antimicrobial treatment. The patient got simultaneous NTX/OLT 4 weeks after EoT but relapsed 8 weeks later.

Adverse events

Adverse events (AEs) were observed in 13 (52%) patients; most common AEs were fatigue, nausea, cephalea, and myalgia/arthralgia. Two NTX/OLT patients had unstable blood pressure at week 2 (SOF/SMV) and week 20 (SOF/DCV), respectively, without need for modification of antihypertensive medication.

Table 2. Overall safety.

		Hemodialysis		Post-NTX		Post-NTX/OLT	
	Total	No cirrhosis	Cirrhosis	No cirrhosis	Cirrhosis	No cirrhosis	Cirrhosis
Patients; *N*	25	6	4	6	2	2	5
AE	13	3	3	1	3	2	1
Grade 3–4 AE	3	1	0	1	1	0	0
SAE	6	2	3	0	1	0	0
Death	0						
Change – IS regimen	1	0	0	1	0	0	0
SOF – reduction	3	1	0	0	2	0	0
RBV reduction	1	1	0	0	0	0	0

NTX, renal transplantation; OLT, orthotopic liver transplantation; AE, adverse event; SAE, severe adverse event; IS, immunosuppressive; SOF, sofosbuvir; RBV, ribavirin.

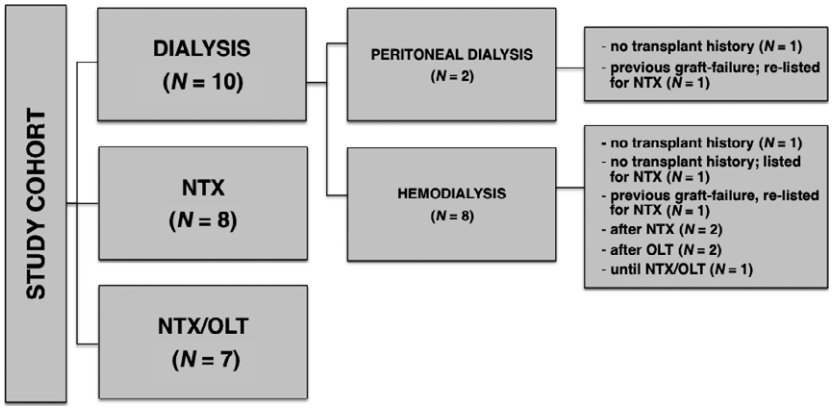

Figure 2 Evaluated study cohort – subgroups. NTX, kidney transplantation; OLT, orthotopic liver transplantation; NTX/OLT, combined kidney-/liver transplantation.

One patient experienced photosensitivity/sunburn (mild; treatment week 4) under SOF/SMV, the patient who failed to use recommended sun protection. One NTX patient suffered from therapy-refractory ascites before the start of antiviral treatment (SOF/DCV) due to spontaneous bacterial peritonitis under antibiotic prophylaxis and needed multiple abdominal paracenteses during therapy as outpatient. A patient on peritoneal dialysis treated with SOF/PR developed hemolytic anemia (hemoglobin nadir: 7.9 mg/dl) despite low ribavirin dose (200 mg/QD) and required red blood cell transfusions 3 times. Due to slow virological response, treatment was prolonged to 16 weeks; the patient achieved SVR12/SVR24. Adverse and severe adverse events according to subgroups are given in Table 2.

Dose reduction

In three patients, SOF dose was reduced (400 mg/QD to 400 mg/48 h): in one HD patient due to sepsis induced pancytopenia; in each one NTX patient because of worsening of general health status and therapy-refractory ascites or due to further renal impairment (creatinine increased from BL to week 2: 2.98 vs. 3.8 mg/dl). SOF reduction was maintained until EoT. Thus, reduction of full-dose SOF regimen based on worsening of renal retention parameters was needed only in one (4%) patient.

Immunosuppressive regimens

Twenty patients were on immuno-suppressive treatment including five patients within the HD cohort after liver transplantation or kidney transplantation before starting antiviral treatment (Fig. 2). Immuno-suppressive regimen was based on calcineurin inhibitors in 16 (80%) patients (cyclosporine [CyA]: 6; tacrolimus [TaC]: 10) and m-TOR inhibitors in the others. Within SIM-treated patients ($N = 9$), seven received immunosuppressive agents (TAC: $N = 6$; everolimus = 1). Levels of immunosuppressive drugs were monitored at weeks 2, 4, 8, 12, 16, 20, and 24, respectively, and were entirely stable under antiviral treatment. Only one patient (SOF/DAC) required dose-adjustment while on treatment (CyA escalation at week 6 [BL: 50 mg/BID to 75 mg/BID] – week 9 after that return to BL dosage until EoT).

Discussion

The main finding of this "real-world" observational study, evaluating IFN-free DAA-based regimens in a real-life cohort of patients with ESRD on hemodialysis or in the post-transplant setting, was the achievement of 96% SVR12 rate. In addition, this study extends the safety of SOF-based regimens in patients after combined liver/kidney transplantation similar to those for NTX recipients [6,7].

SVR rates were accompanied by significant improvement of liver function, similar to findings described by others [28]. Importantly, 88% of patients tolerated full-dose sofosbuvir well, questioning suggested dose-reduction strategies of highly effective antiviral agents. Even the need for dose reductions in two of reported three cases may be debated in retrospect. There are ongoing studies with the combination of SOF/LDV (NCT02503735; NCT02251717), which should shed light on optimal treatment duration and the need of ribavirin.

The available literature on treatment of these patients is scarce, and not a single fully published randomized controlled phase three study has appeared yet. Bhamidimarri *et al.* [4] evaluated treatment of 15

ESRD patients with half-dose SOF in combination with SIM (full dose), resulting in lower SVR12 rates compared with our findings in hemodialysis patients (83% vs. 90%). In a study of Aqel *et al.* [29], seven patients with GFR <30 ml/1.73 m^2/min were included, without giving any further details. For other DAA-combination regimens, findings from the C-SURFER ([5]; elbasvir/grazoprevir) and preliminary data from the RUBY-1 ([4], 2D/3D-combination) trial were published or presented at the ILC/EASL 2015. Both regimens showed excellent antiviral potency combined with acceptable safety profiles; nevertheless, RUBY-1 data are hard to evaluate due to low sample size.

This real-life cohort focused on patients usually excluded from randomized controlled trials due to multiple comorbidities. Treatment performed was highly individualized as concepts according to regimen and duration based on published findings were missing [2,30]. The main rationale to select one specific DAA-based regimen was drug availability at the time of treatment initiation in the absence of evidence-based recommendations or guidelines in patients on high need of antiviral treatment. This approach was highly effective yet. Relatively prevalent rate of hospitalization reflects the severity of underlying disease within this real-life cohort, respectively, but was unrelated to drug toxicity based on DAA-based regimen.

SVR data from randomized controlled studies are important, but data gained from real-life experience, considering safety within the real-life setting, are needed. So far, substantial safety concerns with PR-triple combination within the treatment of first generation protease inhibitors surfaced only from real-life experience [31].

Even before publication of CUPIC data, we investigated whether randomized placebo-controlled trials are comparable to cohorts treated within real-life requirements and found that "selection criteria" had big impact on the final outcome (SVR) [31]. The role of adherence on the effectiveness of SOF-based regimens was evaluated in 4026 US veterans; within this large real-life cohort, SVR rates achieved by SOF/ribavirin at any VA facility were significantly lower than in clinical trials [33].

High efficacy of DAA-combination regimens in patients with chronic kidney disease may enliven discussion whether antiviral treatment should be initiated in renal transplant candidates but when treatment should be initiated. The possibility that successful antiviral HCV treatment may result in disadvantages for patients listed for kidney transplantation may be of concern but neglected in developed countries.

One might speculate that in future, there is discussion about allocating grafts from HCV-positive donors to HCV-negative ESRD recipients [34]. To answer these questions, more data are needed to offer sufficient answers, and moreover, ethical issues are to be debated. However, there are no data whether HD patients listed for kidney re-transplant should be treated with DAA-combination therapy preferably. So far, safety data as well as data on drug–drug interactions are missing within these populations.

The limitation of the study is the heterogeneity of treatment schedules used. Nevertheless, there was a common denominator, namely the use of full-dose sofosbuvir. The variety of treatment regimens selected reflects the rapid changing landscape of HCV drugs. In this observational cohort, the treatment regimens used were mainly determined by the rules of the local insurance companies, which changed with each drug approved. Furthermore, the treatment recommendations of AASLD and EASL were modified four times during the observational period and none of them covered the treatment of patients with impaired kidney function.

Our results, although retrospectively assessed, showed that the majority of patients with CKD even on HD but also after renal transplantation tolerated the concept of full-dose SOF-based regimens (400 mg/QD) well, which is confirmed by a case series published by Hundemer GL *et al.* [35], as well as by Nazario *et al.* [36] treating 17 ESRD patients on hemodialysis or GFR <30 ml/min with the combination of SOF/SMV.

In conclusion, interferon-free full-dose sofosbuvir-based DAA combinations are effective and proved to be overall safe in "real-life" patients on hemodialysis and after NTX or combined NTX/OLT. Low patient number in subgroup analysis and open-label treatment in various DAA combinations precludes firm conclusions regarding treatment in this "special" cohort. Nevertheless, the promising efficacy and safety data of full-dose sofosbuvir warrant further evaluation in larger study and real-life populations.

Authorship

SB: participated in acquisition, analysis and interpretation of data; study concept; statistical analysis; and drafting of the manuscript. RAZ, KK, CF, RS, and AFST: acquired the data. RST, MS, HZ, BW, AS, MT, and HH: critically revised the manuscript for important

intellectual content. PF and AM: participated in study concept and design; analysis and interpretation of data; and drafting of the manuscript.

Financial disclosures/conflict of interest

SB received speaker's honoraria from Bristol Myer-Squibb and is a member of advisory board of AbbVie. KK, CF, RaZ, RAST, AFST, BW, and ASCH have nothing to declare. RUST is a member of advisory board of Gilead, AbbVie, Bristol Myer-Squibb, MSD, and Janssen and received speaker honoraria from Gilead and unrestricted research grant from MSD and AbbVie. MST is a member of advisory board of AbbVie, MSD, Bristol Myer-Squibb, and Gilead and received speaker's honoraria from Bristol Myer Squibb, Gilead, and AbbVie. HZ received honoraria for consulting and lecturing from AbbVie, Bristol Myer-Squibb, Gilead, Jannsen, and MSD. MT received grants from MSD, honoraria for consulting from AbbVie, Gilead, Janssen, and MSD, and payments for lectures from Bristol Myer Squibb, Gilead, MSD, and Roche.

PF is a member of advisory board of AbbVie, MSD, Bristol Myer-Squibb, Gilead, and Roche, and received speaker's honoraria from BMS, Gilead, AbbVie, and Roche and unrestricted research grant from Roche and Gilead. HH received lecture fees from AbbVie, MSD, Bristol Myer-Squibb, Gilead, and Janssen, is an advisory board member of AbbVie, MSD, Bristol Myer-Squibb, Gilead, and Janssen, and received unrestricted research grant from AbbVie. AM: is a member of advisory board of: AbbVie, MSD, Bristol Myer-Squibb, and Gilead, and received speaker's honoraria from Bristol Myer-Squibb, Gilead, and AbbVie and unrestricted research grant from Roche, Gilead, and MSD.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Liver- and kidney function – at baseline and 12 weeks after end of daa-based antiviral treatment.

Table S2. Renal retention parameters on antiviral treatment with daa-based regimens.

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