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Efficacy and safety of direct-acting antivirals for treatment of hepatitis C infected kidney transplant recipients; a meta-analysis

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ABSTRACT

The use of direct-acting antivirals (DAAs) for treatment of hepatitis C virus (HCV) infection has been shown to very effective. However, its efficacy and tolerability in kidney transplant recipients are unclear. A literature search was performed using MEDLINE, EMBASE, and Cochrane Databases from inception through January 2017. We included studies that reported crude numbers of kidney transplant patients who achieved sustained virological response (SVR) or developed adverse effects with DAA therapy. Pooled estimated rates of SVR at 12 weeks (SVR12) after DAA therapy and discontinuation rate of DAAs treatment with 95% confidence interval (CI) were assessed using a random-effect, generic inverse variance method. The study protocol is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42017054575). Around, 24 studies with 892 kidney transplant recipients were included in the meta-analysis. The pooled estimated SVR12 rate with DAAs treatment for HCV among kidney transplant patients was 97% (95% CI: 95%-99%; $I^2 = 22\%$). The pooled estimated rate of discontinuation of DAAs treatment for HCV among kidney transplant patients was 2% (95% CI: 1%-3%; I2 = 0%). Reported treatment-related serious adverse events included bradycardia with syncope in the co-administration of sofosbuvir with amiodarone, pulmonary embolism, gastrointestinal bleeding, portal vein thrombosis, bacteremia, anemia particularly with regimens including ribavirin, and uncommonly increased serum creatinine. The findings of our study suggest excellent efficacy and tolerability profiles of DAA therapy for HCV infection in kidney transplant patient populations.

Mini-Review

Implication for health policy/practice/research/medical education:
The efficacy and tolerability of direct-acting antivirals (DAAs) therapy for HCV infection in kidney transplant recipients are unclear. In this meta-analysis including 24 studies with 892 kidney transplant recipients, we demonstrate excellent efficacy and tolerability profiles with estimated SVR12 rate of 97% and estimated rate of discontinuation of DAAs of 2%.

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Introduction

Hepatitis C virus (HCV) infection universally affects greater than 200 million people worldwide (1). Transmission of HCV occurs essentially via blood transfusion. Consequently, the prevalences of HCV infection in end-state kidney disease on hemodialysis (2.6%-22.9% in Western countries) and in kidney transplant recipients (1.8%-8% in developed countries) are higher than in the general population (~1% in the United States) (2-5). Most kidney transplant patients have received HCV infection while on dialysis. Transmission from organ transplantation is a scarcity in this current era due to decent donor screening (6).

In the current years, remarkable advancement has been made in the development of oral anti-HCV agents that undeviatingly inhibit and target multiple HCV viral proteins with interferon (IFN) free direct-acting antiviral (DAA) therapies with excellent reported sustained

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virologic response (SVR) at 12 weeks with smaller side effects (1,7,8).

Since DAAs do not stimulate the host immune system, which is a main concern of IFN therapy, studies have implied that DAAs can be utilized for the eradication of HCV infection following renal transplantation (1,9-11). However, its efficacy and tolerability in kidney transplant recipients are unclear. Thus, we conducted a meta-analysis to assess the efficacy (SVR 12) and safety of DAA therapy for HCV infection in kidney transplant recipients.

Materials and Methods

Search strategy

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (12). The study protocol is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42017054575). W.C. and C.T. (two investigators) independently searched published articles and conference abstracts listed in MEDLINE, EMBASE and the Cochrane databases from inception through January 2017 using the following words: " direct-acting antiviral" AND "transplantation" AND "kidney" or "renal" (Item S1 in online supplementary data). A manual search for additional relevant studies using references from retrieved articles was also performed. Differing decisions were resolved by mutual consensus.

Inclusion criteria and outcomes

The inclusion criteria were 1) observational studies or randomized controlled trials (RCTs) published as original studies or conference abstracts that evaluated the efficacy and safety of DAAs for treatment of HCV infection in kidney transplant populations and 2) crude number of kidney transplant patients who achieved SVR or developed adverse effects with DAA therapy were provided.

Our outcomes of interest in this study included the efficacy of DAA treatment representing by pooled rate of SVR and serious adverse side effects requiring DAA discontinuation representing by pooled rate of DAA discontinuation.

Data extraction

A structured data collection report utilized to derive the data from included studies consisted of the first author, country where studies were conducted, type of study, year of publication, total number of kidney transplant patients, HCV genotype, baseline estimated glomerular filtration rate (eGFR) (mL/min/BSA), DAA regimens, time between transplant to DAA treatment, duration of DAA treatment, SVR12, reported adverse events and drug-related serious adverse events, adverse event details, change in renal function with DAA treatment, changes in immunosuppression (dose changes during DAA treatment), rate of treatment discontinuation due to serious adverse events.

Statistical analysis

MetaXL software (EpiGear International Pty Ltd) (13) was used for meta-analysis of efficacy and safety of DAA treatment. A random-effect model was employed rather than a fixed-effect model, given the high likelihood of between-study variances. Statistical heterogeneity was appraised using Cochran's Q test. This statistic was complemented with the I^2 statistic, which quantifies the proportion of the total variation crossed studies that is due to heterogeneity rather than chance. An I^2 of 0%–25% renders insignificant heterogeneity, 26%–50% low heterogeneity, 51%–75% moderate heterogeneity and >75% high heterogeneity (14). The likelihood of publication bias was evaluated by funnel plots of the logarithm of odds ratios vs. their standard errors (15).

Results

The search strategy yielded 643 potentially relevant articles: 540 were excluded based on the title and abstract which apparently showed that they did not fulfill inclusion criteria regarding study design, article type, population, or outcome of interest (Figure 1). The remaining 103 articles underwent full-length review, with 79 excluded because they were not observational studies or RCTs (n = 10) or did not report outcomes of interest (n = 69). Twenty-four studies (1,10,11,16-41) with 892 kidney transplant recipients were included in the meta-analysis. Table 1 and Table 2 contain individual characteristics of all included studies.

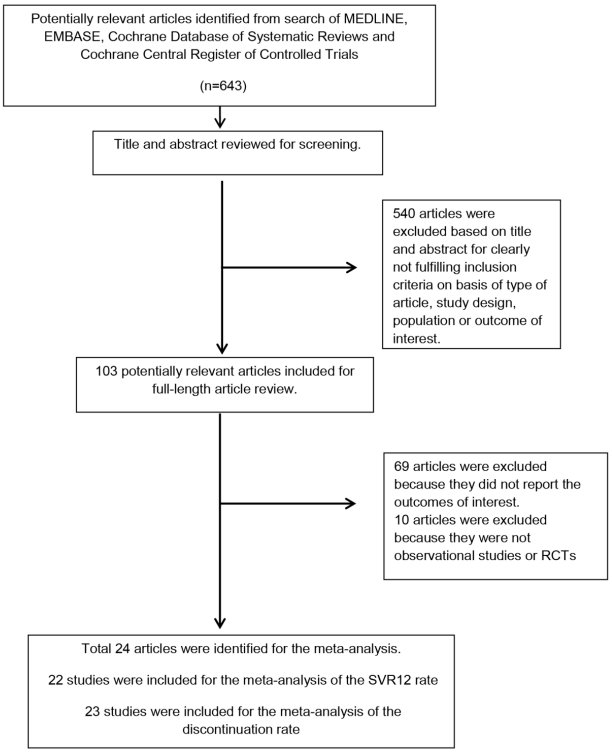

Figure 1. Search Strategy.

Table 1. Main characteristics of studies of HCV treatment with DAAs in kidney transplant recipients

Authors	Country	Type of study	Year	Total (N)	Genotype	Baseline eGFR (mL/min/BSA)	Treatment	Time between transplant to HCV treatment	Duration of treatment (weeks)	SVR12
Kamar et al (16)	France	Cohort	2016	25	76% (I)	1.3±0.6; eGFR 64±21	SOF+SIM (n=6), SOF+LDV (n=9), SOF+ DCV (n=4), SOF+RBV (n=3), SOF+ LDV +RBV (n=1), SOF+SIM+RBV (n=1), PegIFN+SOF+RBV (n=1)	146 months (range 1–329)	12 weeks (76%) or 24 weeks (24%)	100%
Sawinski et al (11)	USA	Cohort	2016	20	88% (I)	1.39±0.43; eGFR 63.44±20.81	SOF + SIM (n=9), OF + LDV (n=7), OF + RBV (n=3), OF + DCV (n=1)	888 days (IQR 341–1621 days).	12 weeks	100%
Lin et al (6)	USA	Multicenter-cohort	2016	24	58% (Ia), 17% (Ib), 12.5% (non-subtypable), 12.53% (II)	1.21 (0.66–1.76); eGFR 71.9 (47–96)	37% SOF + SIM (n=9), 2.5% SOF+SIM+RBV (n=3), 29% SOF + LDV (n=7), 4% SOF+ LDV +RBV (n=1), 17% SOF+RBV (n=4)	96 months (range 2 to 492)	12 to 24 weeks	91%
Beinhardt et al (17)	Austria	Cohort	2016	8 Ktx alone, 7 Ktx/Ltx	13.3% (Ia), 53.3% (Ib), 13.3% (IIIa), 6.7% (IVa/c/d), 6.7% (IVh) 6.7% (Ib/IIIa)	Ktx alone; 1.8±1.0/eGFR 62.7±38.3 Ktx/Ltx; 1.3±0.3/eGFR 81.2±24.6	Ktx alone, SOF+LDV (n=1), OF+SMV (n=3), OF+DCV (n=5), CV + SMV (n=1), Ktx/Ltx, SOF+ SIM (n=3), SOF+DCV (n=4)	>1 year after transplant	12 weeks (80%) or 24 weeks (20%)	100%
Colombo et al (10)	Italy, France, Austria and Germany	RCT	2016	114	15% (Ia), 75% (Ib), 2% (no confirmed subtype), 9% (IV)	Median creatinine clearance 56 (35–135)	SOF + LDV	12.0 (0.5–42.0) years	12 weeks (50%) or 24 weeks (50%)	100%
Goyal et al (18)	USA	Cohort	2016	8 KT alone, 10 pts Ktx/Ltx	89% (I)	All; 1.23±0.38 Ktx alone; 1.28±0.5 Ktx/Ltx; 1.18±0.27	SOF+LDV (n= 6), SOF+SIM (n=7), SOF + RBV (n=4), BV+ PTV-r (n=1)	84 months (7 to 456)	N/A	89%, Ktx alone 87.5%, Ktx/Ltx 90%
Gentil et al (19, 20)	Spain	Multicenter cohort	2016	119 KTRs, 110 KT alone,9 Ktx/Ltx	66.5% (Ib), 3.4% (Ia), .5% (III), 5.9% (IV), 4.2% (II), 2.5% (not notified)	1.41	91% SOF based regimen, 65/119 SOF+ LDV, 17/119 SOF+SIM, 16/119 SOF+DCV, 10/119 SOF+RBV, 9/119 with 3D, 1/119 SIM+DCV+RBV	11.4 ± 10 years	14.1 ± 5 weeks	97.8%
Gallegos-Orozco et al (21)	USA	Cohort	2016	7	85.7% (I), 14.3% (II)	All had eGFR>30	5 with genotype I with SOF+ LDV +/-RBV, One with genotype IIb with SOF+DCV	165 days (range: 109 - 209 days)	12-24 weeks	100%
Hussein et al (22)	Iraq	Cohort	2016	3	100% (IV)	N/A	SOF +RBV	N/A	24 weeks	100%
El-Halawany et al (23)	USA	Cohort	2016	15	93.3% (I), 6.7% (IIa)	N/A	SOF +RBV	N/A	24 weeks	N/A
Fernández et al (24)	Spain	Cohort (Spanish registry)	2016	103	83% (I), 6% (III), 8% (IV), 2% (V)	1.7 (0.58 -8.84)	57% SOF + LDV, 17% SOF + DCV, 41% used RBV	147 (1-561) months	12-24 weeks	98%
Kirushnan et al (25)	India	Cohort	2016	20	60% (I), 30% (III), 5% (IV), 5% (mixed)	1.41±0.54	SOF +RBV	12.5 years	12 weeks	76.9%

Table 1. Continued

Prasad et al (26,27)	India	Cohort	2016	22	63.6% (III), 27.3% (I), 4.5% (II), 4.5% (IV)	N/A	SOF + RBV (n=14), SOF + RBV+DCV (n=5), SOF + RBV+ LDV (n=3)	N/A	24 weeks for SOF + RBV; At least 12 weeks for SOF + RBV+DCV or SOF + RBV+ LDV	100%
Kusnir et al (28,29)	USA	Cohort	2016	21	Almost all (I)	N/A	SOF+ LDV +RBV (n=13), SOF+ LDV (n=5), SOF+DCV (n=1), SOF+SIM (n=1), SOF + RBV (n=1)	60-90 days after transplant	12 weeks	100%
Lubetzky et al (30,31)	USA	Cohort	2016	31	90.3% (I), 6.5% (II), 3.2% (III)	1.3 ± 0.4; eGFR 64.2±16.5	Genotype I, SOF+ LDV (n=21, 75%), SOF + LDV + RBV (n=3,11%), SOF + RBV (n=2, 7%), SOF+ DCV (n=2, 7%); Genotype II, SOF + RBV (n=2); Genotype III, SOF+DCV (n=1)	Median of 1,168 (range 101, 10404) days	93.5% 12 weeks 6.5% 24 weeks for 2 patients with SOF+ LDV	97%
Martin et al (32)	USA	Cohort	2016	21	57% (Ia), 38% (Ib), 5% (Ie/Ig)	1.41 ± 0.5	SOF + RBV, SOF SIM, LDV /SOF + RBV	N/A	N/A	95%
Aull et al (33)	USA	Cohort	2016	29	85% (I)	37% >60 mL/min, 15% 50-59, 19% 40-49, 11% 30-39, 11% 20-29, 7% Unknown	63% SOF+LDV, 11% SOF+LDV+RBV, 11% SOF+SMV, 4% OBV+PTV-r +DSV+RBV, 4% SOF+RBV, 4% SOF+DCV+RBV, 3%SOF+DCV	29 months post-transplant (range 2-122)	Majority 12-24 weeks	86% at the time of analysis (6/7)
Polanco Fernandez et al (34)	Spain	Cohort	2016	33	N/A	N/A	SOF + LDV (90.9% [n= 30]) or DCV (9.1% [n= 3]	N/A	N/A	100% at the time of analysis (11/11)
Fernandez Ruiz et al (35)	Spain	Cohort	2016	48	N/A	N/A	SOF+ LDV (87.5% [n = 42]) or SOF+DCV (6.3% [n = 3]), and DSV +OBV +PTV-r (6.3% [n = 3]), RBV in 56.3% (n = 27)	9.3 years (IQR 6.4-14.0)	N/A	100% (13/13)
Sawinski et al (36,37)	USA	Cohort	2016	43, 19 HCV+ donor, 24 HCV- donor	90.7% (I), 9.3% (II)	1.39 (IQR 1.07-1.73)	23/43 SOF+ LDV, 4/43 SOF+ LDV +RBV, 4/43 SOF + RBV, 12/43 (12%) SOF+SIM	1123 (428-1738) days in HCV+ donor, 1064 (340-2840) days in HCV- donor	1/43 16 weeks 3/43 24 weeks 39/43 12 weeks	100%
Hatahet et al (38)	USA	Cohort	2016	11	90.9% (IA) 9.1% (II)	1.4	73% LDV +SOF, 18% SOF+SIM, 9% SOF+RBV	13 months (range 6-124 months)	N/A	91%
Snyder et al (39)	USA	Cohort	2016	16	100% (I)	N/A	SIM/SOF/RIBA, SOF/LED/RIBA and SOF/LED and SIM/, SOF	N/A	N/A	100%
Trakroo et al (40)	USA	Cohort	2015	8	100% (I)	All >30 mL/min	SOF+SIM (n=2), SOF+ LDV (n=6)	N/A	12 weeks	N/A
Kogiso et al (41)	Japan	Cohort	2016	7	100% (I)		DCV+ asunaprevir	5 (0.5-35) years after transplant	24 weeks	100% (5/5)

Abbreviations: Adverse events (AEs); Estimated glomerular filtration rate (eGFR); Hepatitis C virus (HCV); Ledipasvir (LDV); Paritaprevir-ritonavir (PTV-r); Simeprevir (SIM); Sofosbuvir (SOF); Ombitasvir (OBV); Dasabuvir (DBV); Daclatasvir (DCV); Grazoprevir-Elbasvir (GZR-EBR); Velpatasvir (VEL); Ribavirin (RBV); Serious adverse events (SAEs); Not available (N/A).; Kidney transplant (Ktx); Liver transplant (LTx); Calcineurin inhibitor (CNI).

Table 2. Reported adverse effects, renal safety and discontinuation rate of HCV treatment with DAAs in kidney transplant recipients

Authors	Reported AE and Drug related SAE	AE details	Change in renal function	Change in IS (dose change during DAA treatment)	Treatment discontinuation due to SAEs	Comments
Kamar et al (16)	0% No adverse event was observed.	Hemoglobin level remained unchanged during therapy	No significant change in kidney function was observed. At the end of therapy, GFR had decreased by 10 mL/min or greater in 3 patients: One having at baseline eGFR of 30 mL/min and two others having initially a GFR of 87 and 93 mL/min, respectively.	Doses of tacrolimus remained unchanged during and after therapy. Tacrolimus trough levels significantly decreased during therapy and did not increase after therapy cessation. No modification to cyclosporine or everolimus dose or level occurred	0%	N/A
Sawinski et al (11)	6/20 (30%)	2/20 anemia; 1/20 anemia requiring blood transfusion; 4/20 increased Serum Cr (>0.25 mg/dL) due to supratherapeutic tacrolimus levels, diuretics, and losartan. No rejection was observed.	No statistically significant differences in serum Cr before and after treatment.	9/20 (45%) IS dose change; 3/9 (33.3%) increased IS dose; 6/9 (66.7%) decreased IS dose; CNI levels decreased after completion of DAA therapy, regardless of CNI dose alteration during the course of antiviral treatment.	0%	N/A
Lin et al (1)	11 patients (46%) AE; 3 SAE; 1- GI bleeding; 1- portal vein thrombosis and streptococcus bacteremia; 1- sinus bradycardia with syncope (co-administration of SOF and amiodarone); 1- Shortness of Breath; 1- Gout flair; 1- Fatigue; 1- Headache; 1- Dizziness; 1- Diarrhea; 1- Pain in the lower extremity; 1- Photosensitivity; 1- Rash; 1- Insomnia	No rejection related to the treatment.	No significant change in kidney function was observed	Calcineurin inhibitor trough levels did not significantly change during therapy. One patient had a lower tacrolimus level post-treatment and one patient required dose adjustment during a hospitalization for dizziness.	0%	N/A
Beinhardt et al (17)	KTx alone; AE- 4; SAE- 1 (refractory ascites received OLT); Ktx/Ltx; AE- 3; SAE- 0 Most common AEs fatigue, nausea, cephalgea, and myalgia/arthalgia	1 KTx alone (refractory ascites received OLT); 2 Ktx/Ltx had unstable BP at week 2 (SOF/SMV) and week 20 (SOF/DCV), without need for modification of antihypertensive medication	Not significant after treatment (12 weeks) in both KTx alone and Ktx/Ltx	KTx alone-1 (SOF/DAC while on CyA; needed to increase does by 50%)	0%	N/A

Table 2. Continued

Colombo et al (10)	78 (68%) AE; 3/114 (2.6%) SAE 1- Syncope 1- increased Cr 1- Pulmonary embolism	No episodes of rejection occurred The most frequent adverse events overall were headache (n = 22 [19%]), asthenia (n = 16 [14%]), and fatigue (n= 11 [10%]). Grade 3 or 4 laboratory abnormalities; Hemoglobin deficiency 2/114; Lymphocytopenia 2/114; Neutropenia 1/114; Thrombocytopenia 1/114; Leukopenia 1/114; International normalized ratio 1/114; Creatinine level 2/114; Lipase level 3/114; Hyperglycemia 1/114; Hyponatremia 1/114; Hyperuricemia 10/114; Urine blood level 3/114; Glycosuria 2/114	Renal function remained stable in most patients, both during study treatment and up to posttreatment week 4 (median change in creatinine clearance [eGFR by Cockcroft–Gault equation], -0.6 to -3 mL/min) None of the 8 patients who had creatinine clearance less than 40 mL/min at baseline had a reduction in creatinine clearance to less than 30 mL/min during therapy.	21 patients (18%) required adjustment in there IS regimen. Thirteen of the 21 required dosage adjustment to manage immunosuppressant levels, 4 to align the dosage with the site's policy for managing immunosuppressants, 3 to address suspected drug–drug interactions, and 1 because of a skin eruption. 10 patients CNI dose increased; 2 patients CNI dose decreased; 1 patients both CNI reduced and increased	1/114 (0.9%) 2/114 (1.8%) Temporary discontinuation	DAA discontinuation due to syncope from interaction with amiodarone treatment.
Goyal et al (18)	One patient had AKI secondary to CyA toxicity No other major adverse effects.	No rejection	Mean serum creatinine remained unchanged ($P = 0.5$)	7/18 (39%) IS dose change Tacrolimus dose increase was required in 5/13 patients and CyA dose was decreased in 2/3.	0%	N/A
Gentil et al (19, 20)	28/119 cases (23.5%), above all anemia (12) or cytopenia (4) related to RBV.	N/A	Serum creatinine (Cr) levels at the end of the treatment showed a minimal and nonsignificant increase: 1.51 mg/dL versus 1.41 mg/dL (P ¼ .09); proteinuria was not modified either: 1076 versus 856 mg/24 h (P ¼ .5).	The tacrolimus dose tended to increase slightly over the course of the treatment, with a non-statistically significant 2.60±1.82 mg/d at the end of the treatment versus 2.32±1.70 mg/d at the beginning ($P = 0.17$). Tacrolimus levels did show a significant decrease: 5.89±2.16 ng/mL at the end versus 7.43±1.78 ng/mL pre-treatment ($P < 0.001$), already seen at the fourth week of treatment (6.03±1.964 ng/mL, $P < 0.001$)	7/119 Stopping treatment was necessary in 7 cases; 4 of these were treated with 3D: 2 showed serious neurotoxicity attributable to the drug's interaction with tacrolimus with a major increase in tacrolimus levels, 1 hepatotoxicity, and 1 severe gastrointestinal event. Three patients who were receiving SOF (plus l LDV in 2 cases) and ribavirin showed severe anemia.	Serious problems could be seen in cases of concomitant use of 3D and anti-calcineurin drugs, especially tacrolimus, which question their use or require a very strict and coordinate follow up between hepatologists and transplantation nephrologists.

Table 2. Continued

Gallegos-Orozco et al (21)	Very well tolerated with (2/6) severe adverse events in two of three patients on ribavirin (severe anemia requiring blood transfusions and ribavirin dose reduction) The most frequent adverse events included fatigue (n = 3), headache (n = 2), anemia requiring blood transfusion and erythropoietin injections (n = 2), and nausea (n = 1). Both patients who developed severe anemia (hemoglobin < 8 g/dl) was on ribavirin.	N/A	All of the patients have functioning grafts at six months to one-year post-renal transplant.	N/A	0/6 (0%)	N/A
Hussein et al (22)	Well tolerated. No major adverse events. Two patients required blood transfusion and temporary RBV dose reduction due to anemia 12 weeks after the initiation of treatment.	N/A	Renal function was stable throughout the treatment course and there were no episodes of acute rejection while on treatment.	N/A	0/3 (0%)	N/A
El-Halawany et al (23)	One patient had anemia related to RBV and required dose adjustment with resolution of his anemia.	There were no episodes of graft rejection and none required modification in immunosuppression.	All KT recipients had either stable or improved creatinine during treatment of their HCV.	N/A	0% (0/15)	N/A
Fernández et al (24)	Grade 2 or 3 anemia appeared in 14 (33%) RBV and 9 (15%) without RBV Others adverse events reported were grade 2 and grade 3 hyperbilirubinemia in 4 (4%) and 2 (2%) patients, respectively (all but one in patients taking RBV).	There were 3 episodes of acute humoral graft	No statistically significant differences in the mean level of serum creatinine, eGFR and proteinuria before and after treatment. 17 (16%) patients experienced renal dysfunction (increase in serum creatinine > 25%) during antiviral therapy, of whom 65% were cirrhotic in comparison with only 29% cirrhotic patients who did not develop significant renal dysfunction (P =0.004)	57 (55%) patients required immunosuppression dose adjustment. Tacrolimus doses required adjustments in 47 of the 75 (62.6 %) patients: tacrolimus dose was increased in 34 of 47 and reduced in 13 of 47. This was not significantly associated with a particular regimen of DAAs (P > 0.05). Cyclosporine doses required adjustments in 7 of the 14 patients (50%) receiving a cyclosporine-based therapy (dose reduction in all). Only 6 patients were under everolimus treatment and doses were increased in 2 of them.	0%	A non-negligible number of patients, most of them cirrhotic, developed mild allograft dysfunction and a significant proportion of patients required immunosuppression dose adjustment, warranting a close follow-up during therapy.
Kirushnan et al (25)	The drugs were well tolerated in the majority. 1 patient required erythropoietin temporarily after RBV therapy.	There were no new onset graft dysfunctions indicating no major drug interactions between SOF and immunosuppressants predisposing either to rejection or calcineurin toxicity.	There was no change in the baseline creatinine 2 weeks and 1 month after initiation of therapy.	N/A	0%	N/A

Table 2. Continued

Prasad et al (26,27)	Well tolerated except fall in Hb and one required blood transfusion and 3 required EPO	N/A	No significant change in renal function	Tacrolimus dose was increased in 10 and decreased in 2 to achieve required trough level	0%	N/A
Kusnir et al (28,29)	N/A	Four patients were complicated by antibody mediated rejection while on Therapy (Could be unrelated to the treatment); however immunosuppression levels were also altered)	N/A	(10/21) Tacrolimus dose adjustments were required in 10 patients to maintain therapeutic levels	0%	N/A
Lubetzky et al (30,31)	No serious adverse effects Overall, no significant change in proteinuria before and after therapy Increase in protein to creatinine ratio during and after therapy in 6 patients. Additionally, 2 patients have a GFR now of less than 20. (All of the patients who developed worsening proteinuria received SOF+ LDV)	No serious infections No patients described headache, fatigue, or nausea. Two weeks after completion of therapy, one patient was admitted and treated for pneumonia.	No significant change in renal function	2 patients had a decrease in tacrolimus levels to less than 4 ng/mL that improved with appropriate adjustment by the treating physician. (1 treated with SOF+ LDV+RBV and 1 treated with SOF+ RBV.)	0%	Patients with proteinuria or lower GFR should be monitored more closely. Patients with more than 300 mg/g of proteinuria were significantly more likely to develop worsening proteinuria than those with less than 300 mg/g of proteinuria at the start of therapy (P<0.001). None of the patients with minimal proteinuria had significant changes in proteinuria or serum creatinine levels with therapy. (4/6 had kidney biopsies during or after completion of therapy. Results of these biopsies were variable and included non-specific glomerular changes in 2 cases, diabetic nephropathy in 1 case and moderate IFTA in the fourth case). There was no significant change in Panel Reactive Antibody (PRA) class I or class II post therapy (P=0.45 and P=0.13 respectively).
Martin et al (32)	None of the 21 patients had severe adverse events and none died during treatment.	N/A	The average change in SCr was + 16% (SD = 0.67).	Immunosuppression dosage did not change for 15(71%) patients, it was increased for 2 patients, decreased for 3 patients, and changed in both directions for 1 patient.	0%	N/A
Aull et al (33)	Adverse events included anemia requiring RBV dose reduction or discontinuation (n=2), headache (n=2), acute kidney injury due to tacrolimus toxicity, diarrhea, & worsening blood glucose control (n=1 each).	One patient died 4 months after achieving SVR of an unknown cause.	N/A	N/A	2/29 patients self-discontinued DAAs. The first patient self-discontinued it due to high blood pressure and numbness in his mouth. The second had anemia and resulting weakness from the ribavirin and discontinued it on his own.	N/A

Table 2. Continued

Polanco Fernandez et al (34)	0% (0/14)	There were no episodes of acute rejection or other relevant adverse events.	N/A	There were no significant differences in Tac (p= 0.911) or MMF levels (p= 0.785) between baseline and EOT. Tac doses had to be increased in 92.8% (13/14) of patients by a median of 66.0%.	0% (0/14)	N/A
Fernandez Ruiz et al (35)	The treatment was well tolerated, with no episodes of adverse events while on therapy or relevant adverse events.	No episodes of AR while on therapy	There were no differences between baseline and EOT (20 patients) in graft function (50.8 vs. 48.6 mL/min; *P* = 0.293) or 24-hour proteinuria (0.43 vs. 0.38 g; *P* = 0.540).	N/A	0% (0/20)	N/A
Sawinski et al (36,37)	Well tolerated	No significant between proteinuria before or after treatment 0 (0%) rejection during treatment	There were no differences between Cr before and after treatment	Tacrolimus level in the entire cohort (median posttreatment tacrolimus level 4.9 ng/mL, IQR 4.2-6.2 versus median pretreatment tacrolimus level 5.8 ng/mL, IQR 4.9-7.4, *P*=0.02; this difference in tacrolimus levels was driven by the SOF/SIM subgroup. CNI dose changed 16/43; CNI dose increased 6/43; CNI dose decreased 10/43	0% (0/43)	N/A
Hatahet et al (38)	DAA Rxs were well tolerated with the exception of dose modification of ribavirin due to anemia	no episodes of acute rejection There was a significant reduction in proteinuria, with median U p/c ratio pre-DAA Rx of 0.38 mg/g (range 0.05-1.32 mg/g) and median U p/c ratio post-DAA Rx of 0.18 mg/g (range 0.05-0.48 mg/g) (*P*=0.02)	The mean SCr pre and post DAA Rx was similar (1.4mg/dl)	N/A	0% (0/11)	N/A
Snyder et al (39)	N/A	There were no episodes of acute cellular rejection.	N/A	N/A	N/A	N/A
Trakroo et al (40)	There were no adverse events requiring cessation of therapy.	There were no episodes of graft rejection and none required modification in immunosuppression.	All KT recipients had stable renal and liver function during and after the completion of therapy	N/A	0%	N/A
Kogiso et al (41)	One case was dropped out due to mild fever and renal impairment.	N/A	The other cases showed no severe adverse events in liver or renal function.	The tacrolimus concentration was maintained and no substantial dose adjustment was required.	1/7	N/A

Abbreviations: Estimated glomerular filtration rate (eGFR); Hepatitis C virus (HCV); Ledipasvir (LDV); Paritaprevir-ritonavir (PTV-r); Simeprevir (SIM); Sofosbuvir (SOF); Ombitasvir (OBV); Dasabuvir (DBV); Daclatasvir (DCV); Grazoprevir-Elbasvir (GZR-EBR); Velpatasvir (VEL); Ribavirin (RBV); Serious adverse events (SAEs); Not available (N/A); Kidney transplant (Ktx); Liver transplant (LTx); Calcineurin inhibitor (CNI).

Efficacy of DAAs for treatment of HCV-infected kidney transplant recipients

Of 24 studies, 22 were included in the analysis to assess the effectiveness of DAA treatment for HCV infection among kidney transplant recipients as shown in Table 1. Details regarding HCV genotype, baseline eGFR, DAA regimens, time between transplants to DAA treatment, duration of DAA treatment of each included study were provided in Table 1. The estimated SVR12 rate with DAAs treatment for HCV among kidney transplant patients was 97% (95% CI: 95%-99%; I^2=22%), as demonstrated in Figure 2.

Safety of DAAs for treatment of HCV-infected kidney transplant recipients

Of 24 studies, 23 were included in the analysis to assess the safety of DAA treatment for HCV infection among kidney transplant recipients as shown in Table 2. Reported adverse events and drug-related serious adverse events, adverse event details, change in renal function with DAA treatment, changes in immunosuppression, rate of treatment discontinuation due to serious adverse events of each included study were provided in Table 2. Reported treatment-related serious adverse events included bradycardia with syncope especially co-administration of sofosbuvir (SOF) with amiodarone (1,10), pulmonary embolism (10), gastrointestinal bleeding (1), portal vein thrombosis (1), bacteremia (1), anemia especially with regimens including RBV, and uncommonly increased serum creatinine (10,18). The estimated rate of discontinuation of DAAs treatment for HCV among kidney transplant patients was 2% (95%CI: 1%-3%; I^2=0%), as demonstrated in Figure 3.

Evaluation for publication bias

Funnel plots to appraise publication bias regarding the efficacy and safety of DAA treatment in recipients with DAA treatment for HCV infection are presented in Figure S1-S2. Overall, the publication bias was insignificant.

Discussion

In this meta-analysis of 892 kidney transplant recipients, we showed an excellent efficacy of DAA therapy for treatment of HCV infection among kidney transplant recipients with overall estimated SVR12 rate of HCV after DAA therapy in kidney transplant recipients of 97%. Besides, DAA therapy in kidney transplant recipients is well-tolerated with an overall estimated discontinuation rate of 2%.

Before the development of DAA therapy, the use of IFN-based treatment for HCV infection has been restricted to pretransplant administration due to concerns related to acute allograft injury, immune stimulation related allograft rejection, allograft loss, and poor tolerability (1,9). Also, IFN-based regimens have unfortunately been limited in efficacy and poorly tolerated in the end stage renal disease patients (9). Recently, Studies have demonstrated that novel DAA-based antiviral therapies are efficient for HCV patients with stage 4–5 chronic kidney disease with SVR as high as 89% to 94.3% (8,42,43). In this current study, we demonstrated an excellent efficacy of the use of DAAs in post-kidney transplantation setting with pooled estimated SVR12 of 97%.

Despite favorable safety and tolerability profile of DAAs treatment for HCV among kidney transplant patients with only 2% rate of discontinuation of treatment, there are several cautions of DAA therapy and drug-drug interactions bear mention. One of the major reported serious adverse effects was bradycardia with syncope (1, 10). Amiodarone is a known inhibitor of P-GP transport, and SOF is partially cleared via the P-GP system (44). A decreased in P-GP activity means patients taking amiodarone could be exposed to higher levels of SOF,

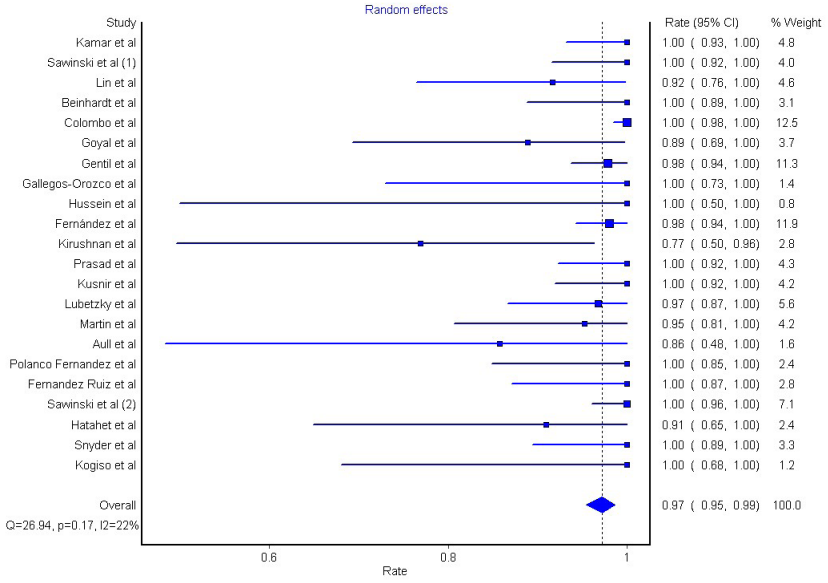

Figure 2. Forest plot of SVR12 rate of DAAs for treatment of HCV among kidney transplant patients.

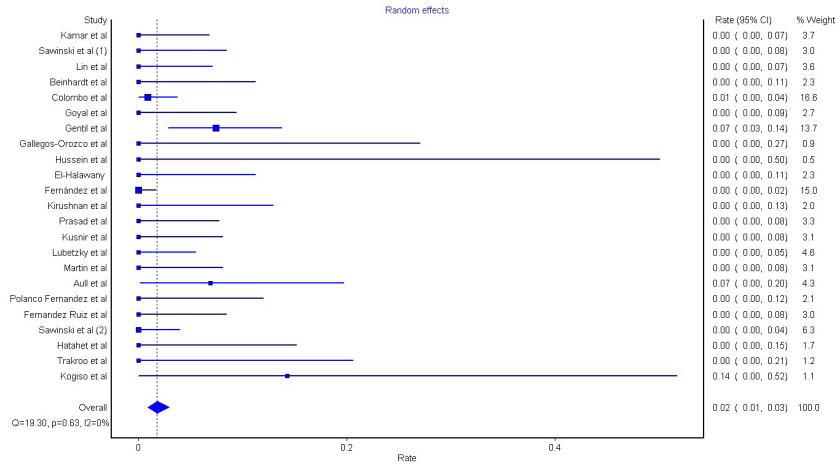

Figure 3. Forest plot of discontinuation rate of DAAs for treatment of HCV among kidney transplant patients.

which is thought to be the cause of bradycardia. Thus, excellent communication between patients and physicians with transplant center are very important to avoid potential drug-drug interactions (10). In addition, drug-drug interactions between DAA and immunosuppression need to be carefully considered. Calcineurin inhibitor (CNI) levels have been shown to fluctuate during and even after DAA treatment is completed (1,10,11,16-41).

Conclusion

In summary, our meta-analysis shows excellent efficacy and tolerability profiles of DAA therapy for HCV-infected kidney transplant recipients. HCV infection should no longer be a major concern among kidney transplant recipients.

Limitations of the study

There are several limitations of our meta-analysis. First, almost all included studies were observational studies with various DAA regimens. Thus, we can only demonstrate an overall efficacy and tolerability of DAA therapy for HCV infection among kidney transplant recipients. Recently, Colombo et al (10) conducted a multicenter RCT evaluating efficacy and safety of the combination of SOF and LDV in kidney transplant recipients for total of 12 weeks or 24 weeks of treatment. They found this SOF and LDV combination effective and well tolerated among patients with kidney transplantation (Table 1). Second, the majority of patients in the included studies had HCV genotype I, leading to limiting the generalizability of the results to other HCV genotypes. Finally, HCV-infected kidney transplant recipients in most included studies received DAA therapy later than 3 to 6 months post-transplantation. The data on the efficacy and safety of DAA therapy during immediate post-kidney transplant, however, were lacking in the included studies in our meta-analysis.

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Authors' contribution

All authors had access to the data and a role in writing the manuscript. All authors read and signed the final paper.

Conflicts of interest

The authors declare that they have no conflicting interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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Supplementary Materials

Supplementary Data contains search strategy and Figures S1-S2.

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