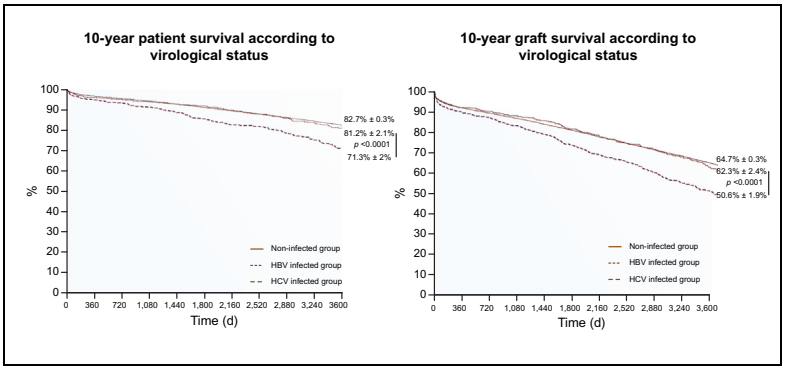
Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Control of replication of hepatitis B and C virus improves patient and graft survival in kidney transplantation

Graphical abstract



Highlights

- Chronic HBV infection no longer influences 10-year patient or graft survival in kidney transplant recipients.
- Chronic HCV infection still negatively impacts 10-year patient and graft survival.
- The negative effect of chronic HCV infection is removed by sustained viral suppression.
- Antiviral therapy should be systematically proposed for HBV- and/or HCV-infected kidney transplant recipients/candidates.

Authors

Hélène Fontaine, Laurent Alric, Julien Labreuche, ..., Stanislas Pol, Alain Duhamel, Philippe Mathurin

Correspondence

philippe.mathurin@chru-lille.fr
(P. Mathurin)

Lay summary

Previously, infections with hepatitis B or hepatitis C virus led to poor outcomes in kidney transplant recipients. However, the outcomes of kidney transplants in patients with viral suppression are as good as those for kidney transplants in non-infected patients. Antiviral therapy should be systematically proposed to hepatitis B and/or hepatitis C-infected kidney transplant recipients or candidates to prevent the deleterious hepatic and extrahepatic impact of chronic viral replication. Recent access to direct-acting antivirals in patients with hepatitis C virus and renal dysfunction provides exciting new opportunities.

http://dx.doi.org/10.1016/j.jhep.2018.12.036

Research Article
Viral Hepatitis

JOURNAL OF HEPATOLOGY

Control of replication of hepatitis B and C virus improves patient and graft survival in kidney transplantation

Hélène Fontaine[1], Laurent Alric[2], Julien Labreuche[3], Benjamin Legendre[4], Alexandre Louvet[4], Corinne Antoine[5], Christophe M. Legendre[6], Marc Hazzan[7], Nassim Kamar[8], Sebastien Dharancy[4], Stanislas Pol[1], Alain Duhamel[3], Philippe Mathurin[4,*]

[1]*Unité d'hépatologie, Hôpital Cochin, Assistance Publique – Hôpitaux de Paris, INSERM U-1223 et USM20, Institut Pasteur Université Paris Descartes, Paris, France;* [2]*Service de Médecine Interne-Pôle Digestif UMR 152, CHU de Toulouse, France;* [3]*Unité de Biostatistiques, France;* [4]*CHRU de Lille, France, Service des maladies de l'appareil digestif, Université Lille 2 and Inserm U795, France;* [5]*Agence de la biomédecine, Saint-Denis, France;* [6]*Service de Transplantation Rénale Hôpital Necker, Paris, France;* [7]*CHRU de Lille, France, Service Néphrologie, Université Lille 2, France;* [8]*Service Néphrologie Hôpital Purpan, Toulouse, France*

Background & Aims: Before antiviral therapy, kidney transplant recipients infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) had poor outcomes. Since the 90s, nucleos(t)ide analogues have been widely used in HBV-infected patients, while interferon-based therapy was rarely used in HCV-infected patients. The aim of this study was to assess the impact of HBV and HCV on patient and graft survival, according to viral replication status.

Methods: Data from January 1993 to December 2010 were extracted from the French national database CRISTAL. A total of 31,433 kidney transplant recipients were included, of whom 575, 1,060 and 29,798 had chronic hepatitis B, C, or were not infected, respectively.

Results: Ten-year survival was lower in HCV-infected (71.3%) than in HBV-infected (81.2%, $p = 0.0004$) or non-infected kidney transplant recipients (82.7%, $p < 0.0001$). Ten-year kidney graft survival was lower in HCV-infected (50.6%) than in HBV-infected (62.3%, $p < 0.0001$) or non-infected kidney transplant recipients (64.7%, $p < 0.0001$). A random analysis of the medical records of 184 patients with HBV and 504 patients with HCV showed a control of viral replication in 94% and 35% of cases, respectively. Ten-year patient and graft survival in patients with detectable HCV RNA was lower than in their matching controls. Conversely, patients with HCV and undetectable HCV RNA had higher 10-year survival than their matched controls without significant differences in graft survival.

Conclusions: Chronic HBV infection does not impact 10-year patient and kidney graft survival thanks to control of viral replication with nucleos(t)ide analogues. In kidney transplant recipients infected with HCV, patients with detectable RNA had worse outcomes, whereas the outcomes of those with undetectable RNA were at least as good as non-infected patients. Thus, direct-acting antivirals should be systematically offered to HCV-infected patients.

Lay summary: Previously, infections with hepatitis B or hepatitis C virus led to poor outcomes in kidney transplant recipients. However, the outcomes of kidney transplants in patients with viral suppression are as good as those for kidney transplants in non-infected patients. Antiviral therapy should be systematically proposed to hepatitis B and/or hepatitis C-infected kidney transplant recipients or candidates to prevent the deleterious hepatic and extrahepatic impact of chronic viral replication. Recent access to direct-acting antivirals in patients with hepatitis C virus and renal dysfunction provides exciting new opportunities.

Introduction

Kidney transplantation is the best treatment for patients with end-stage renal disease (ESRD) because of a significant survival benefit conferred compared to patients who remain on haemodialysis.[1] Although the prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection in patients with ESRD has significantly declined over time, it remains at least 4-times higher than in the general population.[2,3] Chronic HCV or HBV infection can result in chronic liver disease, cirrhosis, and hepatocellular carcinoma[4–6] and increase the risk of chronic kidney disease (CKD).[7–10] Before the use of antiviral therapy, HBV and HCV infection were associated with a poor outcome in kidney transplant recipients (KTRs).[11–14] This poorer outcome has been reported in untreated patients.[11–14] With the development of new treatments against viral hepatitis, an update of data in large cohorts of KTRs with long-term follow-up is warranted.

HBV treatment has improved in the last 2 decades.[15–17] The probability of undetectability HBV DNA upon therapy has increased from the use of first generation (lamivudine or adefovir)[18–20] treatment to the second generation analogues (tenofovir or entecavir).[21,22] Most KTRs infected with HBV have received this safe long-term treatment with analogues before

Keywords: Kidney transplant recipients; chronic hepatitis C; chronic hepatitis B; Prognosis.
Received 29 June 2018; received in revised form 13 December 2018; accepted 17 December 2018; available online 14 March 2019
* Corresponding author. Address: Service Maladies de l'Appareil digestif, Hôpital Huriez, Rue Polonovski, F-59037 Lille cedex, France. Tel.: +33 3 20 44 55 97; fax: +33 3 20 44 55 64.
E-mail address: philippe.mathurin@chru-lille.fr (P. Mathurin).

and continue long after kidney transplant. However, the impact of viral replication on kidney transplant outcomes remains somewhat controversial.[23] Additional studies in HBV-infected KTRs are needed with longer follow-up, larger sample populations, and prospective designs to provide accurate evaluation.

During the same period, interferon-based regimens were contraindicated in KTRs with HCV due to the high risk of transplant rejection. KDIGO recommendations were to treat patients on haemodialysis,[24] but interferon-based regimens were associated with a low efficacy[25] and poor tolerance in patients with ESRD.[25–28] Since 2017, the updated KDIGO and international guidelines recommend extensive use of the new direct-acting antivirals (DAAs) because of their good efficacy and safety.[29,30]

The aims of the present study were to assess the influence of HBV and HCV on patient and graft survival and to determine the prognostic influence of viral replication in a large prospective French database of KTRs.

Patients and methods

Study conduct

Both scientific Committees from the ANRS (in charge of the research on viral hepatitis) and the ABM (Agence de Biomédecine in charge of graft allocation), 2 French governmental agencies, approved the study. The CNIL (Commission Nationale de l'Informatique et des Libertés), the French government agency in charge of the authorisation for the use of database, allowed the CRHU of Lille to analyse these data on December, 28th 2012 (authorization number: 912384).

Data collection and variables

Data from January 1993 to December 2010 were extracted from CRISTAL, a national database begun in 1993 and administered by the ABM that prospectively collects data on all organ transplant recipients in France along with their outcomes and donor characteristics. Recipient and donor data are entered into the CRISTAL registry by transplant and procurement centres, respectively. Recipient deaths are reported prospectively. The study was performed in accordance with the French law indicating that research studies based on the national registry CRISTAL are part of transplant assessment activity and do not require institutional review board approval. Data are entered into the register by each centre. Data collection is mandatory. Variables potentially associated with outcomes were analysed. Demographic and clinical data were collected at the time of transplantation and annually thereafter. The following variables were analysed: gender of donors and recipients, age of recipients and donor, duration of dialysis, duration of cold ischaemia, underlying nephropathy, year of transplantation, screening of HBV surface antigen (HBsAg), and anti-HCV antibodies. Only adult KTRs (*i.e* age ≥18 years) were included.

Random checking of viral replication in infected HBV and HCV recipients

We randomly selected 191 KTRs with HBV and 511 KTRs with HCV to assess the control of viral replication among the centres with high yearly transplant activities from the CRISTAL database. These numbers were calculated on the basis of the following assumptions: a) for HBV cases, we expected viral replication to be controlled in 70% of patients, a relative precision of 20% in the estimation of this rate (corresponding to a width of 95% CI) and 25% with unavailable virological data. b) for HCV cases, we expected viral replication to be controlled in 20% of patients, a relative precision of 40% in the estimation of this rate and 25% with unavailable virological data. Between 2014 and 2015, research assistants visited the centres of selected recipients to analyse recipients' medical records and recorded the following information in case report forms: results of quantification of HBV DNA viral and/or HCV RNA, antiviral therapy (''yes'' or ''no''), the type of regimen in treated patients, data for diagnosis of cirrhosis such as histological data and/or results of Fibrotest® and Fibroscan®. HBV replication was considered to be controlled if HBV DNA <20,000 units during follow-up, based on the definition proposed by the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines published in 2012 to consider antiviral therapy or classify patients as inactive carriers.[15] RNA was classified as undetectable in patients with HCV in 2 cases: a) spontaneous HCV clearance defined as anti-HCV antibodies and negative HCV RNA; b) sustained virological response defined as undetectable HCV RNA 24 weeks after the end of antiviral therapy in treated patients.

Case-control study of HCV recipients with available HCV RNA data

For each KTR with HCV and detectable or undetectable HCV RNA (cases), we randomly selected 1 to 4 matched controls from the 29,797 non-infected KTRs, with the following matching criteria: gender, age of recipients ± 5 years, duration of dialysis in quartiles calculated for the overall population (<40, 41 to 82, 83 to 206, ≥207 months), quartiles of duration of cold ischaemia (<15.8, 15.8 to 20.4, 20.5 to 28.4, ≥28.5 hours) and year of transplantation ± 5 years. The control groups were randomly matched to case groups using the global optimal matching algorithm.

Endpoints

The primary endpoint was 10-year overall survival and the secondary endpoint was 10-year graft survival. Overall survival was defined as the time from the date of kidney transplant to the date of death from any cause. Patients with repeat renal transplants were also treated as censored cases at the time of the second renal transplant. Graft survival was defined as the time from the date of kidney transplant to the date of graft loss or death from any cause. Graft loss was defined as the need for permanent dialysis or repeat transplantation.

For both overall and graft survival, patients with no information at 10 years were treated as censored cases at the date of the last follow-up and events that occurred after the 10-year follow-up period were not included in analysis.

Statistical analysis

Quantitative variables were expressed as means (standard deviations) or medians (interquartile range) and categorical variables were expressed in numbers and percentages. 10-year overall and graft survival were estimated using the Kaplan-Meier method.

Main baseline characteristics were compared in the overall cohort (n = 31,433 adult KTRs) according to viral status (non-infected, HBsAg positive or anti-HCV positive) using the Chi-square test, 1-way analysis of variance or Kruskal-Wallis test, as appropriate. Comparisons in overall and graft survivals were obtained in relation to viral status using the log-rank test. To identify independent predictors of 10-year overall and graft survivals, we performed univariate and multivariate Cox propor-

tional hazards regression models by including viral status and other main baseline characteristics (gender, age of recipients and donors, duration of dialysis, duration of cold ischaemia, and year of transplantation). For each candidate predictor, the proportional hazards assumption was assessed by examining Schoenfeld residuals plots. The log-linearity assumption for continuous predictors was assessed by examining Martingale residual plots. Since the log-linearity assumption for the age of recipients and donors was satisfied after including both linear and quadratic terms, the effect of both ages was modelled using a polynomial function. All candidate predictors associated with survival at a level of significance of p <0.10 were included in the multivariate Cox regression models. We derived hazard ratios (HRs) from Cox regression models as effect size measures with the 95% CIs.

The percentage of patients treated by antiviral therapy and the percentage of responders to antiviral therapy were compared from random samples of available viral data from KTRs with HBV and HCV, between patients with HBV and viral replication and patients with HCV and detectable RNA using the Chi-square test.

Finally, comparisons of overall and graft survival between KTRs with HCV and their matched non-infected controls were performed separately based on detectable HCV RNA using Cox regression models with the robust sandwich variable estimate to take into account the matched sets.

Statistical testing was performed at the 2-tailed α-level of 0.05. Data were analysed using SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA).

Results

Between January 1993 and December 2010, 32,249 KTRs were entered into the CRISTAL database, and 816 who were <18 years old were excluded from the study (Fig. 1). A total of 31,433 adult KTRs (19,580 men and 11,853 women) were included with a median age, duration of dialysis, and cold ischaemia of 49.4 years, 28.1 months, and 18.8 hours, respectively. Patients were grouped according to virological status (Table 1): 575 KTRs with HBV (HBsAg positive) (1.83%), 1,060 KTRs with HCV (anti-HCV positive) (3.37%), and 29,798 non-infected patients (without anti-HCV antibodies or HBsAg) (94.8%). The 3 groups differed significantly for sex ratio, age, duration of dialysis and cold ischaemia, year of transplantation, and causes of underlying nephropathy (Table 1). The prevalence of HBV decreased after 2003 (the median year of transplantation) from 2.26% to 1.4% (p <0.0001), while the prevalence of HCV remained stable (3.38% *vs.* 3.36%).

Ten-year patient survival (primary outcome)

Ten-year patient survival in KTRs with HCV (71.3%; 95% CI 67.5–75.2%) was significantly lower than in the KTRs with HBV (81.2%; 95% CI 77.1–85.2%, p = 0.0004) and non-infected KTRs (82.7%; 95% CI 82.1–83.2%; p <0.0001) (Fig. 2A). There was no difference in 10-year survival between the HBV and non-infected groups (p = 0.6). In multivariate analysis, male sex, age of KTR, duration of dialysis, anti-HCV antibodies, age of donor, duration of cold ischaemia, and year of transplantation were independently associated with mortality at 10 years (Table 2). The proportion of liver-related deaths were significantly higher in HBV (6.85%; p = 0.01) and HCV (7.29%; p <0.0001) KTRs than in non-infected KTRs (2.33%).

Ten-year graft survival (secondary outcome)

Ten-year graft survival in KTRs with HCV (50.6%; 95% CI 46.8–54.4%) was significantly lower than in those with HBV (62.3%; 95% CI 57.6–67%; p <0.0001) or in non-infected KTRs (64.7%, 95% CI 64.0–65.4%, p <0.0001) (Fig. 2B). There was no difference in 10-year survival between HBV and non-infected groups (p = 0.7). In multivariate analysis, male sex, age of recipient,

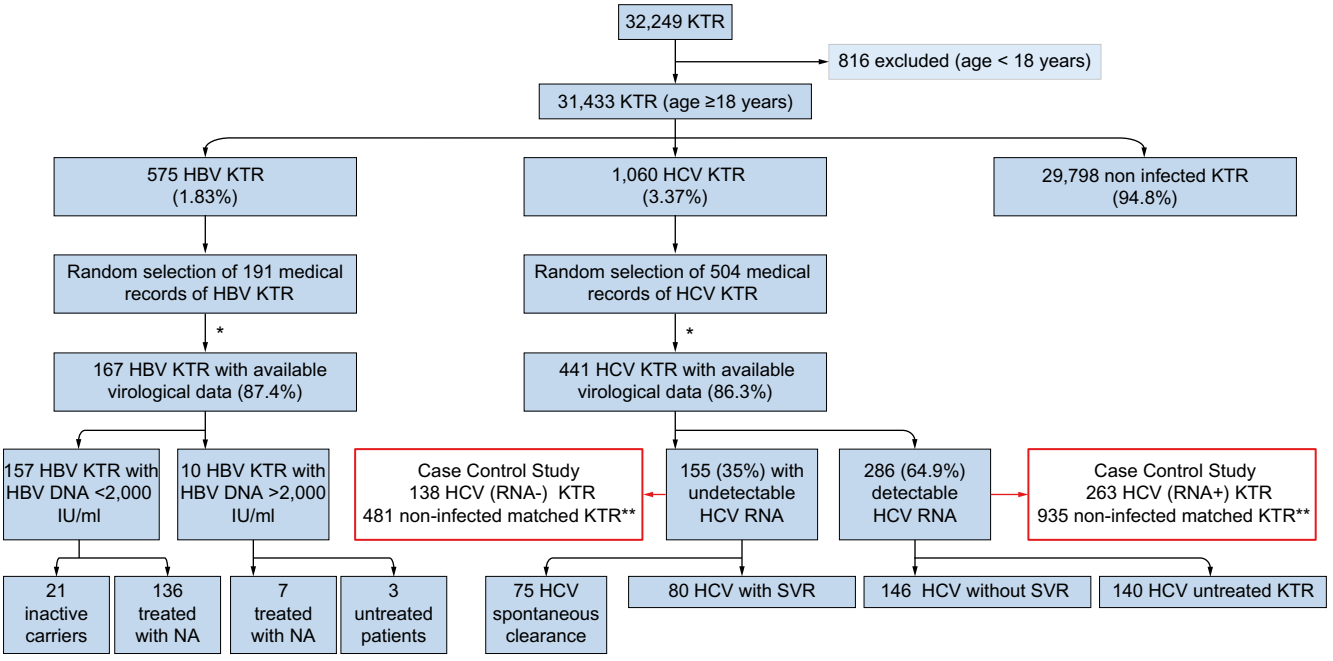


Fig. 1. Flow chart of the study: 32,249 KTRs were entered into the CRISTAL database. A total of 31,433 adult KTRs were included, as 816 who were <18 years old were excluded from the study. HBV, hepatitis B virus; HCV, hepatitis C virus; KTRs, kidney transplant recipients; NA, nucleos(t)ides analogue; SVR, sustained virological response. (This figure appears in colour on the web.)

Table 1. Clinical characteristics according to virological status.

	Virological status			
	Positive HBsAg	Positive anti-HCV	Negative HBsAg and negative anti-HCV	*p* value
Number of patients	575	1,060	29,798	
Male sex, n (%)	420 (73.0)	656 (61.9)	18,503 (62.1)	<0.0001
Age of recipients, mean (SD), years	45.9 (11.8)	48.5 (11.3)	48.4 (13.7)	<0.0001
Duration of dialysis, median (IQR), months	51.1 (25.8–111.4)	78.8 (37.2–188.3)	27.0 (14.5–50.9)	<0.0001
Duration of Cold ischemia, median (IQR), hours	20.0 (15.3–28)	20.0 (14.9–26.5)	18.8 (14.4–24.7)	<0.0001
Age of donors, mean (SD), years	44.3 (14.1)	44.4 (15.4)	45.2 (15.9)	0.13
Year of transplantation, median (IQR)	2001 (1996–2006)	2003 (1999–2007)	2004 (1999–2007)	<0.0001
Underlying nephropathy, n (%)				
Chronic glomerulonephritis	160 (27.8%)	291 (27.4%)	8,079 (27.1%)	
Chronic interstitial nephropathy	40 (7%)	121 (11.4%)	2,947 (9.9%)	
Genetic or congenital	97 (16.9%)	185 (17.5%)	5,897 (19.8%)	
Undetermined and miscellaneous causes[a]	255 (44.3%)	390 (36.8%)	10,865 (36.5%)	
Diabetes	23 (4%)	73 (6.9%)	2,010 (6.7%)	

Values are number (%) unless otherwise indicated.
HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus.
[a] Including mainly hypertensive nephropathy in addition others causes.

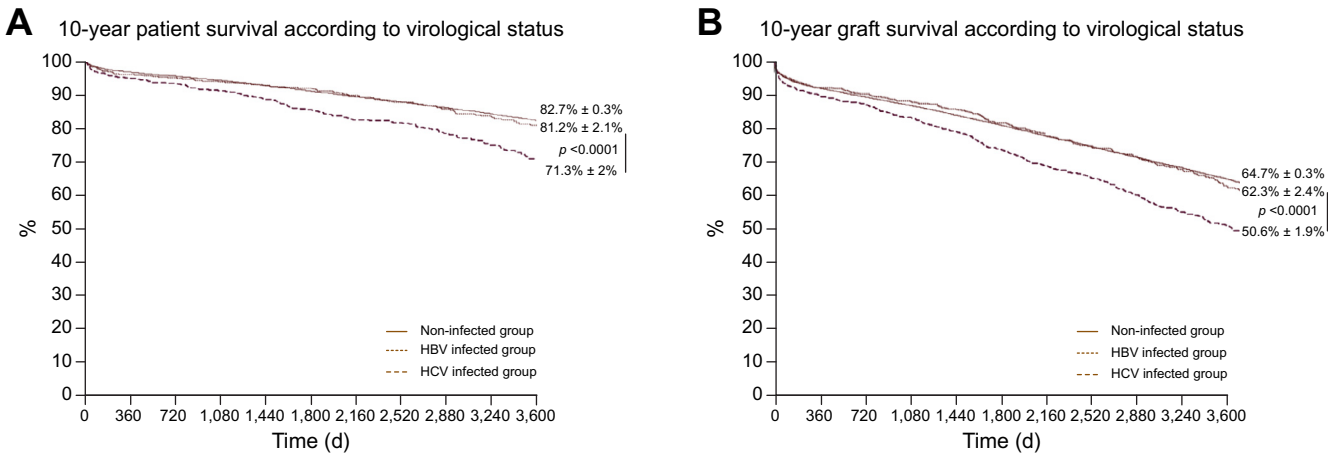


Fig. 2. Ten-year patient and graft survival in HCV-infected, HBV-infected and non-infected KTRs were estimated using the Kaplan-Meier method. (A) Patient survival. (B) Graft survival. HBV, hepatitis B virus; HCV, hepatitis C virus; KTRs, kidney transplant recipients. (This figure appears in colour on the web.)

Table 2. Multivariate analysis of factors associated with 10-year patient mortality in overall cohort.

	Univariate analysis		Multivariate analysis[a]	
Factors	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Male sex, n (%)	1.21 (1.12–1.29)	<0.0001	1.20 (1.11–1.29)	<0.0001
Age of recipients (per 10-year increase)	1.74 (1.69–1.79)	<0.0001	1.67 (1.61–1.74)	<0.0001
Duration of dialysis (per 1 SD log increase)	1.27 (1.22–1.31)	<0.0001	1.26 (1.21–1.31)	<0.0001
Viral status, n (%)		<0.0001		0.0005
Non-infected	1.00 (ref.)	–	1.00 (ref.)	–
HBsAg positive	1.06 (0.84–1.33)	0.62	1.00 (0.78–1.27)	1.00
Anti-HCV-positive antibodies	1.69 (1.46–1.95)	<0.0001	1.38 (1.17–1.63)	<0.0001
Age of donors (per 10-year increase)	1.33 (1.29–1.36)	<0.0001	1.11 (1.07–1.14)	<0.0001
Duration of cold ischemia (per 1 SD log increase)	1.20 (1.15–1.25)	<0.0001	1.07 (1.01–1.14)	0.008
Year of transplantation (per 5-year increase)	1.07 (1.03–1.11)	<0.0001	0.90 (0.85–0.94)	<0.0001

HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; HR, hazard ratio.
[a] Calculated from a multivariable Cox regression model on the basis of the 26,276 patients with non-missing data.

duration of dialysis, anti-HCV antibodies, age of donor, duration of cold ischaemia, and the year of transplantation were independently associated with graft loss at 10 years (Table 3).

Random checking of viral replication in infected HBV and HCV recipients

Virological data were available in 167 out of 191 medical records from KTRs with HBV (87.4%). Viral replication was controlled in 157 out of 167 KTRs with HBV (94%), including 21 inactive carriers and 136 treated with nucleos(t)ides analogues (NAs). In the 10 KTRs with active HBV viral replication, 3 were not treated and 7 were insufficiently controlled by antiviral therapy.

Virological data were available in 441 out of 511 medical records from KTRs with HCV (86.3%) (Fig. 1). HCV RNA was undetectable in 155 out of 441 KTRs with HCV (35%), including 75 with spontaneous HCV clearance and 80 with a sustained virological response after antiviral therapy. HCV RNA was

Table 3. Multivariate analysis of factors associated with 10-year graft failure in overall cohort.

	Univariate analysis		Multivariate analysis[a]	
Factors	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Male sex, n (%)	1.05 (1.00–1.10)	0.030	1.06 (1.00–1.11)	0.024
Age of recipients (per 10-year increase)		<0.0001[b]		<0.0001[b]
Linear term	1.85 (1.67–2.04)	<0.0001	1.82 (1.63–2.04)	<0.0001
Quadratic term	1.08 (1.07–1.10)	<0.0001	1.07 (1.06–1.09)	<0.0001
Duration of dialysis (per 1 SD log increase)	1.18 (1.15–1.21)	<0.0001	1.17 (1.14–1.20)	<0.0001
Viral status, n (%)		<0.0001		<0.0001
Non-infected	1.00 (ref.)	–	1.00 (ref.)	–
HBsAg positive	1.03 (0.88–1.20)	0.68	0.93 (0.79–1.10)	0.38
Anti-HCV-positive antibodies	1.49 (1.34–1.65)	<0.0001	1.30 (1.16–1.45)	<0.0001
Age of donors (per 10-year increase)		<0.0001[b]		<0.0001[b]
Linear term	1.15 (1.07–1.23)	<0.0001	1.02 (0.94–1.10)	0.66
Quadratic term	1.04 (1.02–1.05)	<0.0001	1.02 (1.01–1.03)	<0.0001
Duration of cold ischemia (per 1 SD log increase)	1.19 (1.15–1.22)	<0.0001	1.13 (1.09–1.17)	<0.0001
Year of transplantation (per 5-year increase)	1.01 (0.98–1.03)	0.42	0.91 (0.88–0.94)	<0.0001

HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; HR, hazard ratio.
[a] Calculated from a multivariable Cox regression model on the basis of the 26,276 patients with non-missing data.
[b] Global effect including the linear and quadratic terms.

detectable in 286 out of 441 KTRs with HCV (64.9%), including 140 untreated patients and 146 non-responders to antiviral therapy. In patients with viral hepatitis who were candidates for antiviral therapy (*i.e* with viral replication before initiation of antiviral therapy), KTRs with HBV were more frequently treated than KTRs with HCV (85.6% (143/167) *vs.* 61.7% (226/366); p <0.0001) with greater success (95.8% (137/143) *vs.* 35.4% (80/226); p <0.0001). Using the cut-off of 2,000 IU/ml, the percentage of patients with control of viral replication was lower but not so different to the percentage of patients with control of viral replication using the cut-off of 20,000 IU: 83% *vs.* 94%. The proportion of liver-related deaths among all deaths was 0% in KTRs with HCV and undetectable RNA and 8.93% in KTRs with HCV and detectable RNA. A sensitivity analysis was performed in patients with fibrosis assessment. Assessment of fibrosis was available in 374 out of 702 (53.2%) medical records of infected patients: 93 out of 191 (48.7%) of KTRs with HBV and 281 out of 511 (55%) KTRs with HCV. Assessment of liver fibrosis was performed in 293 (78.3%) cases with histological analysis, in 12 (3.2%) with Fibrotest and in 69 (18.4%) with liver stiffness. Diagnosis of cirrhosis was based on histological analysis or according to cut-offs of non-invasive methods indicating the diagnosis of cirrhosis (0.74 for Fibrotest and 14.6 KPa for Fibroscan). There were no significant differences between patients with fibrosis assessment and those without fibrosis assessment in terms of: male sex (67% *vs.* 62.6%), virological status (21.5% HBV and 78.5% HCV *vs.* 24.7% HBV and 75.3% HCV), duration of dialysis (76.8 *vs.* 87.9 months), duration of cold ischaemia (20 *vs.* 20.8 hours) age of donors (44 *vs.* 45.1 years), patient survival (78.9% *vs.* 73.8%) and graft survival (57.1% *vs.* 52%). Infected patients with fibrosis assessment were younger than those without fibrosis assessment (46.9 *vs.* 49.1 years; p = 0.01). In infected KTRs with fibrosis evaluation, 29 (7.8%) were classified as cirrhotic and 345 (92.2%) as non-cirrhotic. Ten-year patient survival in cirrhotic patients (16.4%; 95% CI 0–36.2%) was significantly lower than in non-cirrhotic patients (84.7%; 95% CI 79.6–89.9%; p <0.0001) with an HR of 7.30 (95% CI 2.3–23.3). Ten-year graft survival in cirrhotic patients (12%; 95% CI 0–27%) was also lower than in non-cirrhotic patients (61%; 95% CI 54.5–67.6%; p <0.0001) with an HR of 3.24 (95% CI 1.5–6.9). The proportion of liver-related deaths was higher in infected KTRs with cirrhosis than in infected KTRs without cirrhosis (64.7% *vs.* 1.8%; p <0.0001). In non-cirrhotic infected patients, 10-year patient survival in KTRs with viral replication (79.9%; 95% CI 72.1–87.6%) was lower than in those without viral replication (89.4%; 95% CI 81.8–96.9%; p = 0.02) with an HR of 2.5 (95% CI 1.3–4.9). Ten-year graft survival in KTRs with viral replication (54.1%; 95% CI 45.1–63.1%) was also lower than in in those without viral replication (70.4%; 95% CI 60.5–80.2%; p = 0.02) with an HR of 1.69 (95% CI 1.1–2.6).

Case-control study

Use of the global optimal algorithm resulted in the random selection of 935 matched non-infected controls for 263 KTRs with HCV and detectable RNA and 482 matched non-infected controls for 137 KTRs with HCV and undetectable RNA. The global optimal algorithm could not identify matched controls for 23 KTRs with HCV and detectable RNA and 18 KTRs with HCV and undetectable RNA. The baseline characteristics of the 2 cases-control studies of KTRs with HCV (detectable and undetectable RNA) are provided (Tables S1 and S2). Ten-year patient survival in KTRs with HCV and detectable RNA (66.1%; 95% CI 61.1–77.1%) was significantly lower than in their matching non-infected controls (81.5%; 95% CI 78.1–84.9%; p = 0.003) with an HR of 1.61 (95% CI 1.18–2.21) (Fig. 3A). Ten-year graft survival in KTRs with HCV and detectable RNA (45.7%; 95% CI 38.2–53.2%) was significantly lower than in their matching non-infected controls (59. 2%; 95% CI 55.3–63.1%; p = 0.01) with an HR of 1.31 (95% CI 1.06–1.61) (Fig. 3B). Ten-year patient survival in KTRs with HCV and undetectable RNA (86.5%; 95% CI 77.8–95.3%) was significantly higher than in their matching non-infected controls (77.9%; 95% CI 72.5–83.4%; p = 0.04) with an HR of 0.50 (95% CI 0.25–0.98) (Fig. 4A). Ten-year graft survival in KTRs with HCV and undetectable RNA (63.8%; 95% CI 52.8–74%) was not significantly different than in their matching non-infected controls (61.5%; 95% CI 55.7–67.3%; p = 0.3) with an HR of 0.84 (95% CI 0.57–1.22) (Fig. 4B). In KTRs with HCV, we conducted a *post hoc* secondary analysis adjusted for diabetes as the primary cause of ESRD (Table 1) and for smoking (31.5% of former or current smokers) showing that the deleterious effect of HCV replication remained significant on 10-year patient survival (HR 2.3; 95% CI 1.11–4.8; p = 0.03) and graft survival (HR 1.63; 95% CI 1.04–2.54; p = 0.03).

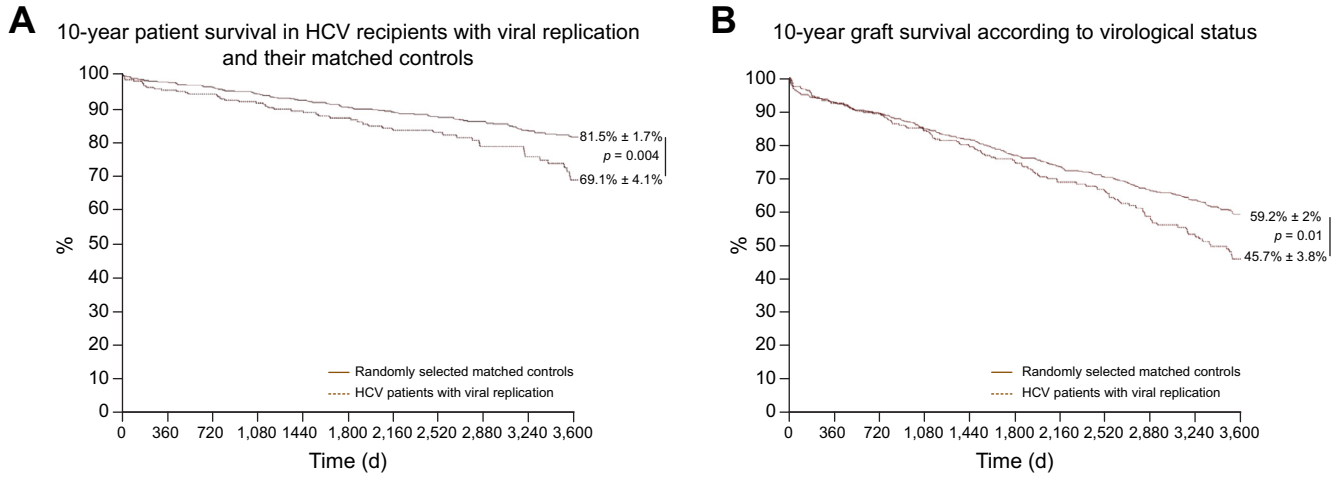


Fig. 3. Ten-year patient and graft survival in KTRs with HCV and viral replication (detectable RNA) and in their matching non-infected controls were estimated using the Kaplan-Meier method. (A) Patient survival. (B) Graft survival. HCV, hepatitis C virus; KTRs, kidney transplant recipients. (This figure appears in colour on the web.)

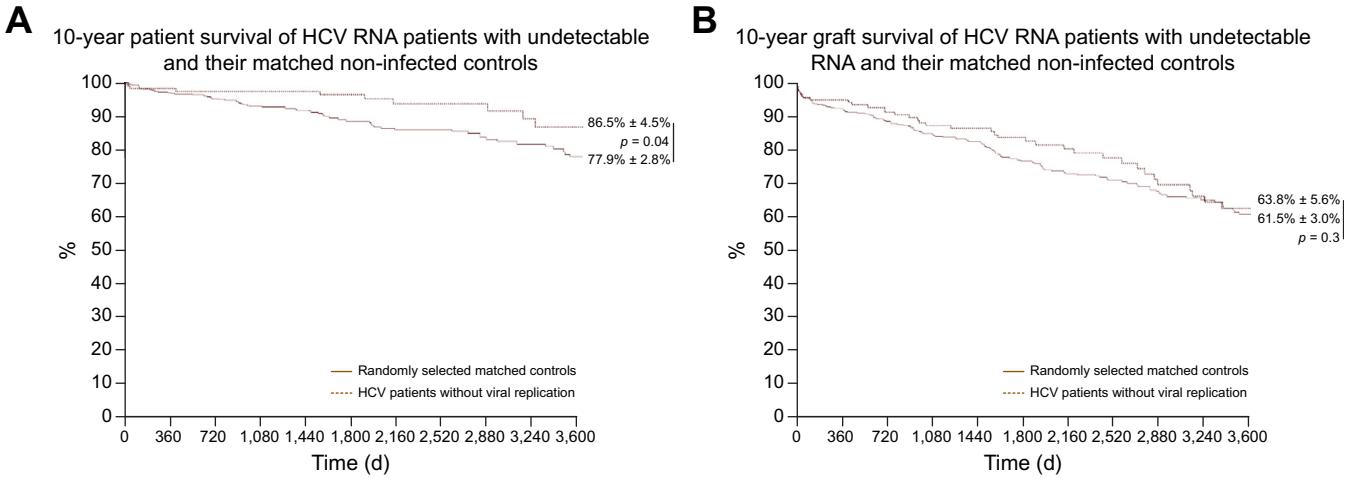


Fig. 4. Ten-year patient and graft survival in KTRs with HCV without viral replication (undetectable RNA) and in their matching non-infected controls were estimated using the Kaplan-Meier method. (A) Patient survival. (B) Graft survival. HCV, hepatitis C virus; KTRs, kidney transplant recipients. (This figure appears in colour on the web.)

Discussion

This study demonstrates that chronic HBV infection, which had previously a negative impact on patient and grant survival in kidney transplantation, no longer influences 10-year patient or graft survival because of the control of viral replication in 90% of cases, related to the extensive use of NAs.[16,17] By contrast, chronic HCV infection still negatively impacts 10-year patient and graft survival, while this negative influence of HCV is removed by sustained viral suppression, as it is no longer observed in KTRs with undetectable HCV RNA. The present results suggest, in line with the international and KDIGO guidelines, that antiviral therapy should be systematically proposed to HBV- and/or HCV-infected KTRs or kidney transplant candidates to prevent the deleterious hepatic and extrahepatic impact of chronic viral replication.[29,30]

In this study of 31,433 French patients who received kidney transplants between 1993 and 2010, the prevalence of HBV and HCV chronic infection was 1.8% and 3.37%, respectively. HBV prevalence decreases from 2.26% before 2003 to 1.4% thereafter; the HCV prevalence remains stable at approximately 3.4%. The prevalences of HCV and HBV are significantly lower than the 30% and 15% reported in our 2 studies from cohorts transplanted before 1990.[12,13] This decrease is related to universal hygienic precautions in haemodialysis units and systematic anti-HBV vaccination in patients with ESRD. However, the current prevalence of both infection in patients with CKD, including KTRs, is still higher compared to the general population.

In the sensitivity analysis restricted to infected patients with available assessment of fibrosis, infected patients with cirrhosis had the worst outcomes and the value of controlling viral replication was confirmed even in patients with less severe liver injury. However, the results of this sensitivity analysis should be treated with caution because of the limited sample size of the cohort of patients with available evaluation of fibrosis, the nature of *a posteriori* analysis, the important variability in the delay to perform the assessment of fibrosis according to the date of transplantation and the risk of inflated false positive (Type I) errors because of multiplicity of comparison. We did not adjust for multiple comparison given the exploratory nature of this sensitivity analysis restricted to patients with fibrosis assessment. Therefore, we could not exclude false positive findings.

Before the era of NAs, 10-year patient survival and graft survival were worst in KTRs with HBV.[13] In the present study, there was no significant difference in patient and graft survival between HBV and non-infected KTRs, thanks to the extensive use of NAs,[18–21] as shown by the random checking of recipient's medical records. Thus, these data support the benefit of NAs in KTRs with HBV.

In contrast to HBV, HCV continues to negatively influence KTRs. These results are similar to those observed more than 20 years ago.[12,13] However, to further clarify this observation, we checked many patient files to classify KTRs according to viral replication. KTRs with undetectable RNA had higher 10-year patient survival and similar 10-year graft survival as non-infected patients. Conversely, the case-control study clearly shows that KTRs with detectable RNA have lower 10-year patient survival and graft survival than non-infected recipients. These data strongly support the control of viral replication in KTRs with HCV as the best approach to improve patient and graft survival. It should be emphasised that the applicability of antiviral treatment was limited during the era of interferon-based regimens. The use of several DAA regimens in patients with CKD, including KTRs with renal impairment, represents major progress that will allow extensive use of antiviral therapy in kidney transplant candidates and KTRs with HCV.[14] HCV therapies with DAAs are being constantly improved. Three DAA combinations have been approved for dialyzed patients or in patients with ESRD.[31–34] Only the new combination of glecaprevir and pibrentasvir has shown pan-genotypic HCV activity, with a sustained virological response rate of more than 95%[34] and negligible renal excretion. Other DAA regimens may be used in KTRs when the glomerular filtration rate is >30 ml/mn.[35,36] DAA treatment should be systematically proposed before and after kidney transplant in KTRs with HCV replication.

Future studies are needed to confirm what has been previously reported in high-risk population for HCV (intravenous drugs user and men who have sex with men), namely whether systematic antiviral treatment can decrease or even eliminate the incidence of viral hepatitis in dialysis patients and KTRs. A European initiative for HCV elimination (European Hepatology –EASL - and Nephrology association - ERA/EDTA) proposed a programme for "micro-elimination" of HCV in patients with CKD.

The limit of this study was the absence of data concerning the antiviral treatment and its efficacy on the viral replication in all patients collected in the CRISTAL database. We tried to overcome this limitation by performing a case-control study in which virological data and data on antiviral therapies were collected by research assistants who analyse recipients' medical records.

In conclusion, KTRs with HBV and HCV in whom viral replication is controlled have similar patient and graft survival as non-infected patients. Recent access to DAA regimens in patients with HCV and renal dysfunction provides exciting new opportunities.

Financial support

This work was supported by a Hospital-Based Clinical Research Program and a grant from (ANRS) (France Recherche Nord&Sud Sida-HIV Hépatites) without any role.

Conflict of interest

LA reports grants and personal fees from BMS, Gilead, Abbvie, Janssen and MSD. SD reports personal fees from NANOBIOTIX, Intercept, Astellas, Abbvie and Gilead. HF reports personal fees from Abbvie, Gilead, BMS, MSD and Janssen. NK reports honoraria from Astellas, Novartis, Gilead, Octapharma, Chiesi, Fresenius, MSD, Neovii, Sanofi and Shire. CL reports personal fees from Alexion and Novartis. AL reports personal fees from Abbvie, Intercept and Verlyx. PM reports personal fees from Gilead, Abbvie, MSD, Bayer Healthcare, Intercept, Sanofi and Verlyx. All outside the submitted work. All other authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design: HF, LA, JL, AD, PM. Acquisition of data: BL, HF, LA, PM. Analysis and interpretation of data: HF, LA, JL, AD, PM. Drafting of the manuscript: HF, LA, JL, AD, SP, PM. Critical revision of the manuscript for important intellectual content: all the authors. Statistical analysis: JL, AD, PM.

Acknowledgement to French kidney transplantation network (for adult patients)

Dr Gabriel Choukroun and Dr Fabien Saint (Amiens), Dr Thibault Culty et Dr Jean-François Subra (Angers), Dr Didier Ducloux et Dr François Kleinclauss (Besançon), Dr Jean-Marie Ferrière, Dr Pierre Merville, Dr Eric Dobremez (Bordeaux), Dr Georges Fournier, Dr Yannick Le Meur (Brest), Dr Xavier Tillou, Dr Thierry Lobbedez (Caen), Dr Jean-Paul Boiteux, Dr Anne-Elisabeth Heng (Clermont-Ferrand), Dr Philippe Grimbert, Dr Alaexandre de la Taille (Créteil), Dr Luc Cormier, Dr Christiane Mousson (Dijon), Dr Bénédicte Janbon, Dr Jean-Jacques Rambeaud (Grenoble), Dr Antoine Durbach, Dr Jacques Irani (Le Kremlin-Bicêtre), Dr Sébastien Bouye, Dr Christian Noël (Lille), Dr Aurélien Descazeaud, Dr Marie Essig (Limoges), Dr Lionel Badet, Dr Emmanuel Morelon (Lyon), Dr Yvon Berland, Dr Valérie Moal, Dr Eric Lechevallier (Marseille), Dr Georges Mourad, Dr Rodolphe Thuret (Montpellier), Dr Maryvonne Hourmant, Dr Georges Karam, Dr Gwenaëlle Kesler-Roussey (Nantes), Dr Laetitia Albano, Dr Daniel Chevallier (Nice), Dr François Desgranchamps, Dr Denis Glotz (Saint-Louis, Paris), Dr Benoit Barrou, Dr Gilbert Deray (Pitié-Salpétrière, Paris), Dr Christophe Legendre (Necker-Enfants Malades, Paris), Dr Olivier Cussenot, Dr Eric Rondeau (Tenon, Paris), Dr Pascal Blanchet, Dr Joëlle Clauedon (Pointe à Pitre), Dr Thomas Charles, Dr Antoine Thierry (Poitiers), Dr Stéphane Larre, Dr Philippe Rieu (Reims), Dr Karim Bensalah, Dr Cécile Vigneau (Rennes), Dr Dominique Guerrot, Dr Christian Pfister (Rouen), Dr Olivier Dunand, Dr Guillaume Biland, Dr Henri Vacher-Coponat (Saint-Denis, Réunion), Dr Eric Alamartine, Dr Jean-Michel Favre (Saint-Etienne), Dr Bruno Moulin, Dr Nabil Chakfe (Strasbourg), Dr Michel Delahousse, Dr Thierry Lebret (Suresnes), Dr Nassim Kamar, Dr Federico Sallusto (Toulouse), Dr Franck Bruyere, Dr Mathias Buchler, Dr Sylvie Cloarec, Dr Hubert Lardy (Tours), Dr Luc Frimat, Dr Jacques Hubert (Nancy).

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.12.036.

References

[1] Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D. Improved graft survival after renal transplantation in the United States, 1988 to 1996. N Engl J Med 2000;342:605–612.
[2] Isnard Bagnis C, Couchoud C, Bowens M, Sarraj A, Deray G, Tourret J, et al. Epidemiology update for hepatitis C virus and hepatitis B virus in end-stage renal disease in France. Liver Int 2017;37:820–826.
[3] Izopet J, Sandres-Saune K, Kamar N, Salama G, Dubois M, Pasquier C, et al. Incidence of HCV infection in French hemodialysis units: a prospective study. J Med Virol 2005;77:70–76.
[4] Lai CL, Ratziu V, Yuen MF, Poynard T. Viral hepatitis B. Lancet 2003;362:2089–2094.
[5] Poynard T, Yuen MF, Ratziu V, Lai CL. Viral hepatitis C. Lancet 2003;362:2095–2100.
[6] Poynard TBP, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. Lancet 1997;349:825–832.
[7] Fabrizi F, Donato FM, Messa P. Association between hepatitis C virus and chronic kidney disease: a systematic review and meta-analysis. Ann Hepatol 2018;17:364–391.
[8] Lee JJ, Lin MY, Yang YH, Lu SN, Chen HC, Hwang SJ. Association of hepatitis C and B virus infection with CKD in an endemic area in Taiwan: a cross-sectional study. Am J Kidney Dis 2010;56:23–31.
[9] Molnar MZ, Alhourani HM, Wall BM, Lu JL, Streja E, Kalantar-Zadeh K, et al. Association of hepatitis C viral infection with incidence and progression of chronic kidney disease in a large cohort of US veterans. Hepatology 2015;61:1495–1502.
[10] Park H, Chen C, Wang W, Henry L, Cook RL, Nelson DR. Chronic hepatitis C virus (HCV) increases the risk of chronic kidney disease (CKD) while effective HCV treatment decreases the incidence of CKD. Hepatology 2017.
[11] Fabrizi F, Martin P, Dixit V, Kanwal F, Dulai G. HBsAg seropositive status and survival after renal transplantation: meta-analysis of observational studies. Am J Transplant 2005;5:2913–2921.
[12] Legendre C, Garrigue V, Le Bihan C, Mamzer-Bruneel MF, Chaix ML, Landais P, et al. Harmful long-term impact of hepatitis C virus infection in kidney transplant recipients. Transplantation 1998;65:667–670.
[13] Mathurin P, Mouquet C, Poynard T, Sylla C, Benalia H, Fretz C, et al. Impact of hepatitis B and C virus on kidney transplantation outcome. Hepatology 1999;29:257–263.
[14] Morales JM, Fabrizi F. Hepatitis C and its impact on renal transplantation. Nat Rev Nephrol 2015;11:172–182.
[15] EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2012;57:167–185.
[16] EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370–398.
[17] Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016;63:261–283.
[18] Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. N Engl J Med 2003;348:800–807.
[19] Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med 2004;351:1521–1531.
[20] Marcellin P, Chang TT, Lim SG, Tong MJ, Sievert W, Shiffman ML, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. N Engl J Med 2003;348:808–816.
[21] Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z, et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2006;354:1011–1020.
[22] Marcellin P, Heathcote EJ, Buti M, Gane E, de Man RA, Krastev Z, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med 2008;359:2442–2455.
[23] Cosconea S, Fontaine H, Meritet JF, Corouge M, Sogni P, Vallet-Pichard A, et al. Benefits associated with antiviral treatment in kidney allograft recipients with chronic hepatitis B virus infection. J Hepatol 2012;57:55–60.
[24] Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease Kidney Int Suppl 2013;1–150.
[25] Deltenre P, Moreno C, Tran A, Ollivier I, Provot F, Stanke F, et al. Anti-viral therapy in haemodialysed HCV patients: efficacy, tolerance and treatment strategy. Aliment Pharmacol Ther 2011;34:454–461.
[26] Fabrizi F, Dixit V, Martin P, Messa P. Combined antiviral therapy of hepatitis C virus in dialysis patients: meta-analysis of clinical trials. J Viral Hepat 2011;18:e263–e269.
[27] Fabrizi F, Dixit V, Messa P, Martin P. Antiviral therapy (pegylated interferon and ribavirin) of hepatitis C in dialysis patients: meta-analysis of clinical studies. J Viral Hepat 2014;21:681–689.
[28] Fabrizi F, Dixit V, Messa P, Martin P. Pegylated interferon mono-therapy of chronic hepatitis C in the dialysis population: systematic review and meta-analysis. Ther Apher Dial 2015;19:611–621.
[29] EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol 2018;69:461–511.
[30] Hepatitis C Guidance 2018 Update: AASLD-IDSA recommendations for testing, managing, and treating hepatitis c virus infection. Clin Infect Dis 2018.
[31] Bruchfeld A, Roth D, Martin P, Nelson DR, Pol S, Londono MC, et al. Elbasvir plus grazoprevir in patients with hepatitis C virus infection and stage 4–5 chronic kidney disease: clinical, virological, and health-related quality-of-life outcomes from a phase 3, multicentre, randomised, double-blind, placebo-controlled trial. Lancet Gastroenterol Hepatol 2017;2:585–594.
[32] Pockros PJ, Reddy KR, Mantry PS, Cohen E, Bennett M, Sulkowski MS, et al. Efficacy of direct-acting antiviral combination for patients with hepatitis C virus genotype 1 infection and severe renal impairment or end-stage renal disease. Gastroenterology 2016;150:1590–1598.
[33] Roth D, Nelson DR, Bruchfeld A, Liapakis A, Silva M, Monsour Jr H, et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4–5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. Lancet 2015;386:1537–1545.
[34] Gane E, Lawitz E, Pugatch D, Papatheodoridis G, Brau N, Brown A, et al. Glecaprevir and pibrentasvir in patients with HCV and severe renal impairment. N Engl J Med 2017;377:1448–1455.
[35] Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014;370:1889–1898.
[36] Feld JJ, Jacobson IM, Hezode C, Asselah T, Ruane PJ, Gruener N, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. N Engl J Med 2015;373:2599–2607.