Transplantation Reviews xxx (2020) xxx

Contents lists available at ScienceDirect

Transplantation Reviews

journal homepage: www.elsevier.com/locate/trre

Review article

New possibilities on transplanting kidneys from hepatitis C virus positive donors: a Systematic Review

Renske C. van Riet [1], Kiki M. van Dijk *,[1], Martijn W.F. van den Hoogen

Department of Internal Medicine, Erasmus MC, University Medical Centre Rotterdam

Contents

1. Introduction . . . 0
2. Method . . . 0
2.1. Search strategy . . . 0
2.2. Study selection . . . 0
2.3. Data extraction . . . 0
2.4. Quality assessment . . . 0
3. Results . . . 0
3.1. Study selection . . . 0
3.2. Study characteristics and quality assessment . . . 0
4. Discussion . . . 0
4.1. Summary of evidence . . . 0
4.2. Limitations . . . 0
5. Conclusion . . . 0
Acknowledgement . . . 0
Conflict of interest . . . 0
References . . . 0

1. Introduction

The scarcity of kidneys for transplantation results in a high mortality rate for waitlisted patients [1]. In comparison with long-term dialysis, kidney transplantation results in better patient survival [2]. Unfortunately, a lot of allografts are discarded because of an increased risk of transmission of infection, such as the hepatitis C virus (HCV) [3].

Nearly 65% of the kidneys of HCV positive donors were discarded between 2005-2014 [1], since HCV is associated with hepatic and extrahepatic complications. The virus has deleterious consequences in recipients of a kidney transplant, resulting in reduced patient and graft survival [4]. Due to high transmission rates, the viral transmission could result in a chronic hepatitis C infection, with liver diseases such as cirrhosis and even hepatocellular carcinoma as a consequence. Therefore, transplanting kidneys from infective donors into uninfected recipients could be considered unethical.

In the past, antiviral therapy was based on the use of PEG-interferon-a in combination with ribavirin. This treatment resulted in a sustained virologic response in less than 50% of the patients [5]. In contrast, recently developed drugs called direct acting antivirals (DAA) have shown high rates of sustained virologic response in HCV infected patients [6]. Moreover, DAA cause fewer adverse effects and result in shorter treatment duration [7]. Data on the prognosis of these patients remain controversial.

Several studies have analysed the outcomes of transplanting kidneys from HCV positive donors, yet the results are inconsistent. Consequently, the expected clinical course of transplanting these kidneys, especially into an HCV negative recipient, remains uncertain.

The aim of this systemic review is to examine the consequences and possibilities of transplanting kidneys from HCV positive donors to HCV negative recipients in comparison with transplanting kidneys from HCV negative donors.

2. Method

2.1. Search strategy

We selected eligible studies by searching the Pubmed electronic database using the following terms: ("Hepatitis C"[Majr] OR

* Corresponding author at: Erasmus Medical Centre, Doctor Molewaterplein 40, 3015 GD Rotterdam, The Netherlands
E-mail addresses: r.vanriet@erasmusmc.nl (R.C. van Riet), k.m.van_dijk@lumc.nl (K.M. van Dijk), m.vandenhoogen@eramusmc.nl (M.W.F. van den Hoogen).
[1] Both authors contributed equally as first authors.

https://doi.org/10.1016/j.trre.2020.100532
0955-470X/© 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Please cite this article as: R.C. van Riet, K.M. van Dijk and M.W.F. van den Hoogen, New possibilities on transplanting kidneys from hepatitis C virus positive donors: a Systematic Revi..., Transplantation Reviews, https://doi.org/10.1016/j.trre.2020.100532

ARTICLE IN PRESS

"Hepacivirus"[Mesh] OR "Hepatitis C Antibodies"[Mesh]) AND ("Hepatitis C"[tiab] OR "HCV"[tiab]) AND ("Kidney"[tiab] OR "Kidneys"[tiab] OR "Renal"[tiab]) AND ("Kidney Transplantation"[Majr] OR "Renal Replacement Therapy"[Mesh]) AND ("Transplant"[tiab] OR "Transplantation"[tiab]) AND ("Recipient"[tiab] OR "Recipients"[tiab] OR "Donor"[tiab] OR "Donors"[tiab]) AND ("Graft survival"[Mesh] OR "Survival Rate"[Mesh] OR "Viral Load"[Mesh]).We restricted our search to articles published between January 1st 2000 and November 7th 2019.

2.2. Study selection

One of the authors, KD, initially examined the titles and abstracts of the search results. Articles that did not focus on the hepatitis C virus in the context of kidney transplantation were excluded. Subsequently, both authors assessed the full text of the remaining articles for eligibility. We discussed any disagreements and came to a consensus. Based on the residual articles, we put together the following exclusion criteria:

- Articles not written in English
- Case reports
- Articles that discussed multi-organ transplantations
- Articles that did not focus on HCV+ donors transplanting kidneys to HCV- recipients

2.3. Data extraction

Our primary outcome measurement was the difference in patient survival between HCV positive donors transplanting to HCV negative recipients (D+/R-) and a control group of HCV negative donors transplanting to HCV negative recipients (D-/R-). Patient survival is defined as the time between the date of transplant and death, the most recent follow-up date or the end of the study period.

As secondary outcome measurements we looked at graft survival, HCV transmission and the cause of death of the recipients. Graft failure is defined as return to dialysis after transplantation or death with a functioning graft. Apart from the parameters mentioned above, we extracted data on mean follow-up time, testing of donor infectiveness and mean recipient age. We only used data on cause of death if the cause was reported in more than one of the studies, to make an adequate comparison between the selected articles. Testing of infectiveness of the donor using viral load was of relevance because serology cannot discriminate a chronic infection from a cleared infection. The same applies for detecting HCV transmission in the recipients. When available, we also focused on the patient survival of the D+/R- group compared with waitlisted controls.

2.4. Quality assessment

We independently assessed the quality of the selected articles. Table 1 presents the criteria we composed to evaluate the articles. We used the Newcastle- Ottawa Quality Assessment Scale [8] as a guideline to set up the criteria. We excluded articles with a score of 3 "No's" or more.

To prevent confounders, the baseline characteristics of the study population must be clearly defined and the study population must be specified by exclusion criteria. To verify donors were truly infective at time of donation, RNA viral load has to be measured and has to be found positive. Potential confounders such as age and comorbidities required proper adjustment for reliable results. Furthermore, the article must compare an HCV positive donor transplanting to an HCV negative recipient (D+/R-), with an HCV negative donor transplanting to an HCV negative recipient (D-/R-) to come to a well-considered conclusion.

We used the PRISMA checklist as a guidance for the structure of this systemic review [9].

Table 1
Quality assessment tool

	Criteria	Yes/No
1	Was donor HCV infectiveness measured by viral load?	
2	Was the study population clearly defined?	
3	Was there an adjustment for potential confounding variables?	
4	Were the patient exclusion criteria clearly stated?	
5	Did the article compare a D+/R- group with a D-/R- group?	

3. Results

3.1. Study selection

The outcome of the study selection is shown in Figure 1. Our search terms resulted in a set of 158 articles of which 12 remained after selection (see Figure 1). We found three other articles [10–12] that also met our inclusion criteria. These three articles do not have MeSH terms since they are published very recently and for this reason they could not be

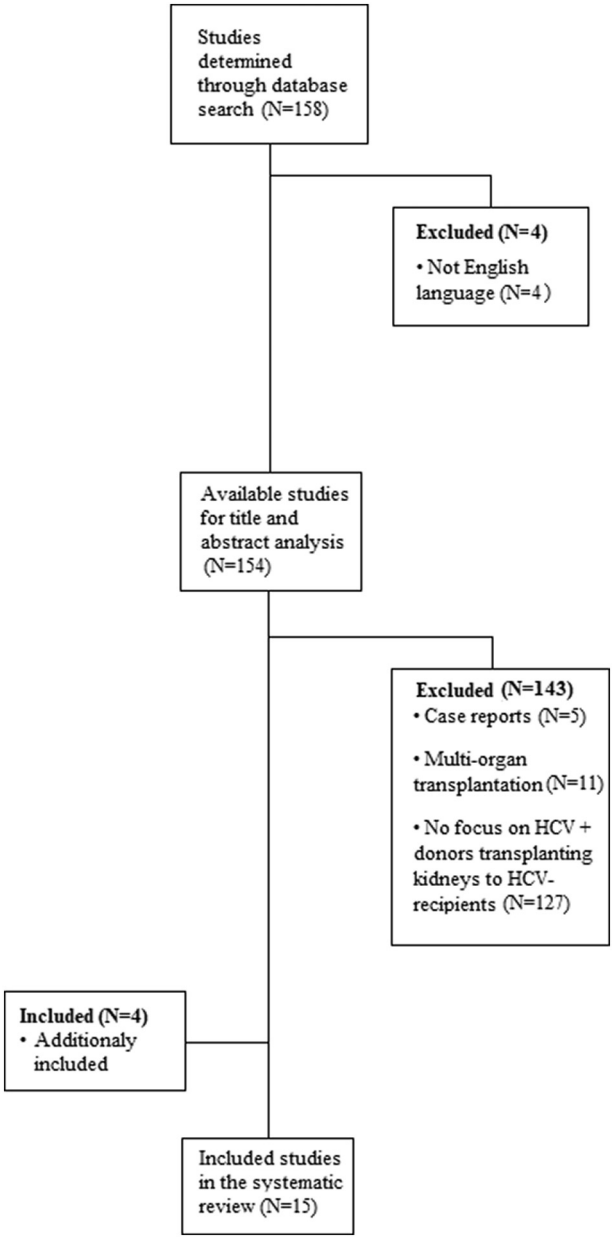

Figure 1. Flowchart

Please cite this article as: R.C. van Riet, K.M. van Dijk and M.W.F. van den Hoogen, New possibilities on transplanting kidneys from hepatitis C virus positive donors: a Systematic Revi..., Transplantation Reviews, https://doi.org/10.1016/j.trre.2020.100532

ARTICLE IN PRESS

Table 2
Quality assessment of the included studies

Study	1	2	3	4	5
Gupta, G., et al.	Yes	Yes	No	Yes	No
Molnar, M.Z., et al.	Yes	Yes	No	Yes	No
Friebus-Kardash, J., et al.	Yes	Yes	No	Yes	Yes
La Hoz, R.M., et al.	Yes	Yes	No	Yes	Yes
Reese, P.P., et al.	Yes	Yes	No	Yes	No
Trotter, P.B., et al.	No	No	No	No	Yes
Durand, C.M., et al.	Yes	Yes	No	Yes	No
Gupta, G., et al.	No	Yes	Yes	Yes	Yes
Goldberg, D.S., et al.	Yes	Yes	No	Yes	No
Morales, J.M., et al.	No	No	No	No	Yes
Singh, N., et al.	No	Yes	Yes	No	Yes
Flohr, T.R., et al.	Yes*	Yes	No	No	Yes
Abbott, K.C., et al.	No	Yes	Yes	Yes	Yes
Bucci, J.R., et al.	No	Yes	Yes	Yes	Yes
Rozental, R., et al.	No	No	No	No	No

* 3 out of 13 donors tested by NAT

found through our search terms. Therefore, we additionally included these articles in our study selection, leading to 15 articles in total.

3.2. Study characteristics and quality assessment

The quality assessment is shown in Table 2. As a result of the quality assessment, we excluded three more articles: Trotter, P.B., et al. [13], Morales, J.M., et al. [14] and Rozental, R., et al. [15]. These studies had three or more "No's".

In sum, we included twelve articles in this systematic review. The study characteristics of these articles are shown in Table 3.

As shown in Table 4, six studies only used NAT to test donor infectiveness [10,12,16–19]. Together, these studies resulted in a total study population of 150 recipients. These 150 recipients had a mean viral transmission rate of 67.3% and a sustained virologic response of 100%. Five of these studies [10,16–19] resulted in a patient survival of 100%. In the study of Gupta, G., et al. [12] one patient died of pneumonia, leading to a patient survival of 98%. La Hoz, R.M., et al [11] reported a 12-month patient survival for the D+/R- group of 100%, compared to 97.2% in the D-/R- group ($p=0.23$).

Five studies reported a lower survival rate of the patients in the D+/R- group in comparison with the D-/R- group. Gupta, G., et al. [3] compared the D+/R- group to matched waitlisted controls as well, and reported a significant better survival for the D+/R- patients. 3-year survival was reported as 84% for the D+/R- group versus 56% for matched waitlisted controls ($p<0.001$). 5-year survival was 68%, respectively 43% ($p<0.001$).

Nine articles gave insight into the number of graft survival. Two articles reported significantly worse graft survival in the D+/R- group [3,20]. One article reported a better graft survival for the D+/R- group, yet this result was not significant [11].

Gupta, G., et al. [3] and Flohr, T.R., et al. [21] reported a transmission rate of 49% respectively 62%. However, four studies reported that the donor HCV was transmitted to all recipients by transplantation [10,16,18,19]. Durand, C.M., et al. [17] and Gupta, G., et al. [12] reported a HCV transmission rate of respectively 50% and 12% after the recipients received pre-transplant prophylaxis with DAAs.

The three most commonly used types of DAA combinations were elbasvir-grazoprevir (EBR-GZR), sofosbuvir-velpatasvir (SOF-VEL), sofosbuvir-ledipasvir (SOF-LDV). One study used glecaprevir-pibrentasvir (GLE-PIB) as DAA treatment [16]. Two studies used ribavirin (RBV) as additional treatment [10,18].

Table 3
Study Characteristics

Authors	Year of publication	Number of patients included	Follow-up time (yr)	Testing of donor infectiveness	Donor HCV genotype
Gupta, G., et al.	2019	D+/R-: n=50	0.23	NAT	1a (n=19) 2a (n=1) 2b (n=1) 3 (n=6) ND (n=23)
Molnar, M.Z., et al.	2019	D+/R-: n=53	Median 0.83 (0.79-0.98)	NAT	1a: n=34 1b: n=1 2: n=3 3: n=15
Friebus-Kardash, J., et al.	2019	D+/R-: n=7	1	NAT	1 (n=4) 1b (n=1) 3a (n=2)
La Hoz, R.M., et al.	2019	D+/R-: n=196* D+/R-: n=352** D-/R-: n=36934	3	NAT* (n=196) Serology** (n=352)	ND
Reese, P.P., et al.	2019	D+/R-: n=20	1	NAT	1 (n=20)
Durand, C.M., et al.	2018	D+/R-: n=10	Median 0.23 (IQR unknown)	NAT (n=9) Undetectable HCV RNA (n=1)	1a: n=3 1a-3: n=1 2: n=1 3: n=1 ND: n=4
Gupta, G., et al.	2017	D-/R-: n= 2105 D+/R-: n=421	Median 0.85 (0.38-8.00)	Serology	ND
Goldberg, D.S., et al.	2017	D+/R-: n=10	Median 0.5 (IQR unknown)	NAT	1a: n=9 1***: n=1
Singh, N., et al.	2012	D-/R-: n=1897 D+/R-: n=118	Mean 6.02 ± 4.26 SD	Serology	ND
Flohr, T.R., et al.	2011	D-/R-: n=90 D+/R-: n=13	Median 1.5 (0.78-6.28)	NAT (n= 3) Unknown (n=10)	ND
Abbott, K.C., et al.	2003	D-/R-: n=34151 D+/R-: n=280	Mean 2.77 ± 1.66 SD	Serology	ND
Bucci, J.R., et al.	2002	D-/R-: n=16337 D+/R-: n=165	Mean 1.85 ± 1.12 SD	Serology	ND

ND = not determined
* Donor infectiveness tested by NAT
** Donor infectiveness tested by serology
*** Subtype unknown

Please cite this article as: R.C. van Riet, K.M. van Dijk and M.W.F. van den Hoogen, New possibilities on transplanting kidneys from hepatitis C virus positive donors: a Systematic Revi..., Transplantation Reviews, https://doi.org/10.1016/j.trre.2020.100532

ARTICLE IN PRESS

Table 4
HCV transmission, survival rates and cause of death of the D+/R- group and D-/R- group

Authors	Mean recipient age (yr) ± SD	HCV transmission to recipients in D+/R- group	Treatment	Graft survival	Patient survival	Cause of death
Gupta, G., et al. (2019)	60	12% detectable HCV RNA, 100% cured	SOF-VEL EBR-GZR	96%	98%	Pneumonia (n=1)
Molnar, M.Z. et al. (2019)	52.6 ± 10.9	100% detectable HCV RNA, 100% cured	Triple therapy (100%) DAA: GLE-PIB (89%) SOF-VEL (9%) SOF-LDV (2%)	100%	100%	-
Friebus-KardashJ., et al (2019)	53	100% detectable HCV RNA, 100% cured	SOF-LDV (43%) SOF-LDV+ RBV (14%) SOF-VEL (43%)	100%	100%	-
La Hoz, R.M., et al. (2019)	52.1 (13.5)	ND	Triple treatment Basiliximab Induction None (9.4%) IL2-RA (13.6%) r-ARTG (56.9%) Alemtuzumab (n=15.4%) Other (n=4.7%)	12-mo: D+/R-:98.4% D-/R-: 94.2% (p=0.17) HR 0.85 [0.25-2.96]	12-mo: D+/R-:100% D-/R-:97.2 % (p=0.23)	ND
Reese, P.P., et al. (2019)	56.3 (6.7)	100% detectable HCV RNA, 100% cured	EBR-GZR (n=17) EBR-GZR + RBV (n=3)	100%	100%	-
Durand, C.M., et al. (2018)	Median age 71.0	50% detectable HCV RNA, 100% cured	Triple therapy (100%) DAA: EBR-GZR (100%) SOF (additional) (20%)	100%	100%	-
Gupta, G., et al. (2017)	55.8 ±12.26	49% (n=62) Seroconverted	MMF/azathioprine (83.3%) TAC (93.3%) Steroids (78.6%)	3-yr: D-/R-: 78% D+/R-: 66% (p<0.001) 5-yr: D-/R-: 65% D+/R-: 44% (p<0.001) HR: 1.76 [1.1-2.05]	3-yr: D-/R-: 87% D+/R-: 76% (p<0.001) 5-yr: D-/R-: 79% D+/R-: 57% (p<0.001) HR: 2.06 [1.7-2.49]	Liver disease: D+/R-: 1.6% Infection: D-R-: 16.2% D+R-: 24.9% (p<0.01)
Goldberg, D.S., et al.(2017)	Median age: 59.0	100% detectable HCV RNA, 100% cured	Triple therapy (100%) DAA: EBR-GZR (100%)	-	100%	-
Singh, N., et al. (2012)	-	-	Azathioprine (24.3%) or mycophenolic acid (73.1%) MMF (100%) Before 1999: cyclosporine (61.5%) After 1999: TAC (22.8%) Prednisone (100%)	10-yr: D-/R-: 48.3% D+/R-: 16.2% (p<0.01) HR: 2.1 [1.6-2.6]	10-yr: D-/R-: 64.8% D+/R-: 22.6% (p<0.01) HR: 2.5 [1.9-3.2]	Liver failure D-/R-: 1% D+/R-: 4% Infection D-/R-: 18% D+/R-: 16% CVD D-/R-: 22% D+/R-: 24%
Flohr, T.R., et al. (2012)	72.0	62% (n=8) detectable HCV-RNA	TAC (100%) MMF (69%) Prednisone (100%)	-	1-yr: D-/R-: 82.3% D+/R-: 46.1% (p<0.008)	Infection D+/R-: 23%
Abbott, K.C., et al. (2003)	47.0 ±12.5	-	Cyclosporine (67.8%) TAC (42.5%) Azathioprine (23.8%) MMF (78.9%) Steroids unknown	1-yr: D-/R-: 93.6% D+/R-: 93.6% HR: 0.77 [0.25-2.42] (p=0.66)	1-yr: D-/R-: 88.2% D+/R-: 74.6% (p<0.01) AHR: 2.30 [1.75-3.26] (p=0.025)	Liver disease D-/R-: 1.5% D+/R-: 6.9% CVD D-/R-: 22.8% D+/R-: 13.2%
Bucci, J.R., et al. (2002)	48.13 ± 11.14	-	Cyclosporine (79.6%) TAC (11.4%) Azathioprine (43.1%) MMF (46.4%)	-	D-/R-:86.4% D+/R-: 69.7% (p<0.01) HR: 1.46 [1.04-2.05] (p=0.028)	Liver disease: D+: 6.6 D-: 0.5% Infection D+: 28% D-: 32% CVD: D+: 56% D-: 49%

Please cite this article as: R.C. van Riet, K.M. van Dijk and M.W.F. van den Hoogen, New possibilities on transplanting kidneys from hepatitis C virus positive donors: a Systematic Revi..., Transplantation Reviews, https://doi.org/10.1016/j.trre.2020.100532

ARTICLE IN PRESS

Several studies described cardiovascular disease (CVD) as the most common cause of death for both the D-/R- as well as the D+/R- group. Another frequently registered cause was infection. Death by liver disease was more often reported in the D+/R- group than in the D-/R- group. Flohr, T.R., et al. [21] reported one death directly caused by HCV liver disease, specifically cholestatic hepatitis.

4. Discussion

4.1. Summary of evidence

This systematic review shows that, since the usage of DAA treatment, kidney transplantations from HCV infected donors to uninfected recipients could result in high graft survival and patient survival rates. Patient survival is superior in the D+/R- group, compared to waitlisted controls. Viral transmission ranged from 12% to 100%, depending on the rate of testing viral load and pre-emptive treatment [10,12,16–19,21].

4.2. Limitations

Initially, we excluded three more articles as a result of the quality assessment. The remaining twelve articles did not meet all of the criteria. However, every study had its individual strengths. Thus, due to the heterogeneity of the studies, we did not attach more importance to one study over another.

Six out of the twelve remaining studies were retrospective observations. These studies depended on databases, which inherently contain errors and shortcomings. Several studies reported missing data on cause of death of the recipients, in some cases leading up to nearly 50% [22]. Additionally, granular data on pretransplant comorbidities of the recipients were not present or not mentioned in the greater part of the studies.

Moreover, we noticed intra-study variance as well as heterogeneity between the studies in demographic characteristics. Bucci, J.R., et al. [22], Singh, N., et al. [20] and Gupta, G., et al. [3] reported more recipients of the African American (AA) race in the D+/R- group. The AA race is widely considered a risk for poorer patient and graft survival. This might be explained by the fact that African Americans have a lower rate of viral clearance and a higher rate of chronic hepatitis C, when treated with PEG-interferon and ribavarin [3]. Other reported demographic inequalities were a longer cold ischemic time and longer pretransplant dialysis for the D+/R- group. On top of that, the recipients of the D+/R- group were older and thus more fragile (e.g. recipients aged >50 y have a risk of 67% increase in fibrosis progression rate [21]).

The elderly were also an inter-study variance. Flohr, T.R., et al. [21] specifically focussed on the elderly recipient population. Therefore, it is quite difficult to compare Flohr, T.R., et al. [21] to the other studies because of the heterogeneity of the study population. The same applies to the race of the recipients, which varies in the different studies.

Additionally, the follow-up time differed between the studies. Five studies had a follow-up time of less than one year [12,16–19]. Hence, they could not report on the long-term outcomes of the transplantation. Data on the outcomes of the trial of Goldberg, D.S., et al. [19] and Durand, C.M., et al. [17] would have been interesting, because the recipients completely cleared the virus. Although the study of Molnar, M.Z. et al. [16] did had a significantly longer follow-up time compared to Goldberg, D.S., et al [16] and Durand, C.M., et al [10], the median follow-up time was less than a year, specifically 302 days. Thus, the study does give a better insight into the patient survival, but a longer follow-up time is still required to demonstrate the long-term outcomes.

Furthermore, only Abbott, K.C., et al. [23] adjusted its results for comorbid conditions. Comorbidities can be an important confounder for patient survival. It is remarkable that in this one study, the patient survival of the D+/R- group is better than in the other studies.

The retrospective data is mostly from an era in which HCV RNA testing was not universally available. Five studies used antibody testing to examine whether the donor was HCV positive. As stated, serology is not precise to determine the infective state of the donor. Donors could have cleared their HCV infection prior to the kidney transplantation. Flohr, T.R., et al. [21] tested only three donors by viral load and La Hoz, R.M., et al. [11] reported on 352 recipients who received a kidney from a donor tested positive by serology. It is possible that not all donors were infective at time of transplantation and therefore HCV transmission rates could be underestimated. Consequently, the risk of using the allografts of those donors is equivalent to HCV negative donors. Therefore the results of these five studies should be interpreted with caution. On top of that, studies that used serology most likely conducted selection bias, because donors of whom they knew were truly infective, were possibly rejected as a donor.

Concerning transmission rates, Durand, C.M., et al. [17] and Gupta, G., et al. [12] used DAA prophylaxis, which could explain the lower HCV transmission rates. The virus could have been cleared before the first time of virus RNA measurement of the recipients in these studies.

The direct acting antivirals are a breakthrough in the treatment of HCV. A study of Pecoraro V., et al. [24] showed that when compared to placebo, treatment with DAAs plus PEG-interferon-a in combination with ribavirin increase the 12 week SVR from 54% to 78% in naïve HCV patients. With DAA treatment, a higher SVR can be achieved, potentially leading to clinical benefits. As can be seen in the included studies, completion of antiviral therapy resulted in a SVR of 100%.

A recently published trial of Franco, A. et al. [25] showed successful transplantations in eleven patients. However, this study did not report on viral transmission and it is therefore unclear whether the recipients were infected in the first place. Since only one donor was evidently NAT positive, merely two recipients have received a kidney from an infective donor. This sample size does not contribute to the data shown by the included studies.

Although the included studies did not focus on the financial aspect of DAA treatment, it should be noted that these drugs are expensive [26]. Currently, it is uncertain who will bear these costs in non-research settings. It should be questioned whether the usage of this viral regimen is ethically justified considering the cost-benefit ratio.

There is still no clear evidence on why the patient survival of the D+/R- group is relatively worse. For HCV negative recipients the donation causes a primary infection, which is likely to be worse in comparison with a donation to HCV positive recipients. Research has shown intrahepatic complications in HCV negative recipients, such as fibrosing cholestatic hepatitis, as well as extrahepatic complications, such as high rates of new onset diabetes after transplantation [27]. On top of that, immunosuppressive therapy could facilitate viral replication [28]. However, an absolute explanation is not found yet [29].

Furthermore, six studies [10,12,16–19] showed a different outcome due to the DAA treatment. Most of these studies only included twenty patients or less, which is why we suggest that these studies are to be repeated in the future, with inclusion of more patients and a control group.

Other disciplines are looking at the use of DAA treatment as well. A recent published trial involving transplantation of hearts and lungs from HCV positive donors into patients without HCV infection, resulted in a prevention of the establishment of HCV infection with DAA treatment for 4 weeks [30].

In the era the other studies were conducted, DAA treatment was not available and antiviral therapy was based on the use of PEG-interferon-a in combination with ribavirin. With this treatment, a sustained virologic response could not be accomplished in 50% of the patients [5]. Consequently, the results of the other six studies could have been different if an antiviral regimen would have been available at that time. A complete clearance of the hepatitis C virus can diminish the several risks reported in the other studies. Further monitoring of the patients who cleared the virus after transplantation is required to analyse the long-term outcomes. Moreover, the timing and especially the length of DAA treatment and the moment of initiation requires more studies.

Please cite this article as: R.C. van Riet, K.M. van Dijk and M.W.F. van den Hoogen, New possibilities on transplanting kidneys from hepatitis C virus positive donors: a Systematic Revi..., Transplantation Reviews, https://doi.org/10.1016/j.trre.2020.100532

ARTICLE IN PRESS

Almost all included articles are from the United States. A significant part of the HCV positive kidney donors from the United States are young, healthy and died of drug overdose [31]. It should be questioned if the positive effect on patient and graft survival (as shown by the article of La Hoz, R.M., et al. [11]) also applies to recipients from other parts of the world, since most other countries might not have comparably healthy and young hepatitis C infective donors. Furthermore, all current infective hepatitis C donors are DAA-treatment naive, and therefore SVR in the recipient is expected to be high. If the donor has shown resistance to DAA (although very uncommon), this might severely hamper effective treatment in the recipient. In these specific cases, we advise against use of these donor organs.

A recent published position statement demonstrates the current literature on this topic [27]. The authors emphasize the possibilities to accomplish a SVR when recipients are treated with pangenotypic direct acting antivirals. They recommend further implementation of D+/R- kidney transplantations, with pre-emptive treatment of DAA, which could ultimately lead to a cost-effective treatment. All in all, the report demonstrates data in line with this systematic review.

5. Conclusion

Despite the high likelihood of viral transmission, acceptance of a kidney from an HCV infected donor can result in superior patient survival compared to remaining on the waiting list. In this era, a sustained virologic response can be achieved with DAA treatment, possibly improving long-term outcomes.

Acknowledgement

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors. No conflict of interest relevant to this manuscript are reported for all authors.

Conflict of interest

The authors have fully disclosed their conflicts of interest in the manuscript and during the submission process. This manuscript has not been published and is not under consideration for publication elsewhere.

References

[1] Reese PP, Abt PL, Blumberg EA, Goldberg DS. Transplanting Hepatitis C-Positive Kidneys. N Engl J Med 2015 Jul 23;373:303–5.
[2] Schnitzler MA, Lentine KL, Burroughs TE. The cost effectiveness of deceased organ donation. Transplantation 2005 Dec 15;80:1636–7.
[3] Gupta G, Kang L, Yu JW, Limkemann AJ, Garcia V, Bandyopadhyay D, et al. Long-term outcomes and transmission rates in hepatitis C virus-positive donor to hepatitis C virus-negative kidney transplant recipients: Analysis of United States national data. Clin Transplant 2017 Oct;31(10):10.1111/ctr.13055. Epub 2017 Aug 19.
[4] Baid-Agrawal S, Pascual M, Moradpour D, Somasundaram R, Muche M. Hepatitis C virus infection and kidney transplantation in 2014: what's new? Am J Transplant 2014 Oct;14:2206–20.
[5] Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL. Jr, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002 Sep 26;347:975–82.
[6] Sawinski D, Kaur N, Ajeti A, Trofe-Clark J, Lim M, Bleicher M, et al. Successful Treatment of Hepatitis C in Renal Transplant Recipients With Direct-Acting Antiviral Agents. Am J Transplant 2016 May;16:1588–95.
[7] Schmidt FP, Zimmermann T, Wenz T, Schnorbus B, Ostad MA, Feist C, et al. Interferon- and ribavirin-free therapy with new direct acting antivirals (DAA) for chronic hepatitis C improves vascular endothelial function. Int J Cardiol 2018 Nov 15;271:296–300.
[8] Wells, G.A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., Tugwell, P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2014; Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed October, 2018.
[9] Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L.A., PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. 2015; Available at: https://systematicreviewsjournal.biomedcentral.com/articles/10.1186/2046-4053-4-1. Accessed October, 2018.
[10] Friebus-Kardash J, Gackler A, Kribben A, Witzke O, Wedemeyer H, Treckmann J, et al. Successful early sofosbuvir-based antiviral treatment after transplantation of kidneys from HCV-viremic donors into HCV-negative recipients. Transpl Infect Dis 2019 Oct;21:e13146.
[11] La Hoz RM, Sandikci B, Ariyamuthu VK, Tanriover B. Short-term outcomes of deceased donor renal transplants of HCV uninfected recipients from HCV seropositive nonviremic donors and viremic donors in the era of direct-acting antivirals. Am J Transplant 2019 Jun 17.
[12] Gupta G, Yakubu I, Bhati C, Zhang Y, Kang L, Patterson JA, et al. Ultra-short duration direct acting anti-viral prophylaxis to prevent virus transmission from hepatitis C viremic donors to hepatitis c negative kidney transplant recipients. Am J Transplant 2019 Oct:25.
[13] Trotter PB, Summers DM, Ushiro-Lumb I, Robb M, Bradley JA, Powell J, et al. Use of Organs From Hepatitis C Virus-Positive Donors for Uninfected Recipients: A Potential Cost-Effective Approach to Save Lives? Transplantation 2018 Apr;102:664–72.
[14] Morales JM, Martinez-Flores JA, Serrano M, Serrano A, Dominguez-Gil B. What are the management issues for hepatitis C in dialysis patients?: renal transplantation from hepatitis C-positive donors. Semin Dial 2014 Sep-Oct;27:459–62.
[15] Rozental R, Bicans J, Shevelev V, Trushkov S, Amerika D. Kidney transplantation from hepatitis C virus positive donors. Transplant Proc 2002 Nov;34:2581.
[16] Molnar MZ, Nair S, Cseprekal O, Yazawa M, Talwar M, Balaraman V, et al. Transplantation of kidneys from hepatitis C-infected donors to hepatitis C-negative recipients: Single center experience. Am J Transplant 2019 Jul 15.
[17] Durand CM, Bowring MG, Brown DM, Chattergoon MA, Massaccesi G, Bair N, et al. Direct-Acting Antiviral Prophylaxis in Kidney Transplantation From Hepatitis C Virus-Infected Donors to Noninfected Recipients: An Open-Label Nonrandomized Trial. Ann Intern Med 2018 Apr 17;168:533–40.
[18] Reese PP, Abt PL, Blumberg EA, Van Deerlin VM, Bloom RD, Potluri VS, et al. Twelve-Month Outcomes After Transplant of Hepatitis C-Infected Kidneys Into Uninfected Recipients: A Single-Group Trial. Ann Intern Med 2018 Sep 4;169:273–81.
[19] Goldberg DS, Abt PL, Blumberg EA, Van Deerlin VM, Levine M, Reddy KR, et al. Trial of Transplantation of HCV-Infected Kidneys into Uninfected Recipients. N Engl J Med 2017 Jun 15;376:2394–5.
[20] Singh N, Neidlinger N, Djamali A, Leverson G, Voss B, Sollinger HW, et al. The impact of hepatitis C virus donor and recipient status on long-term kidney transplant outcomes: University of Wisconsin experience. Clin Transplant 2012 Sep-Oct;26:684–93.
[21] Flohr TR, Bonatti H, Hranjec T, Keith DS, Lobo PI, Kumer SC, et al. Elderly recipients of hepatitis C positive renal allografts can quickly develop liver disease. J Surg Res 2012 Aug;176:629–38.
[22] Bucci JR, Matsumoto CS, Swanson SJ, Agodoa LY, Holtzmuller KC, Peters TG, et al. Donor hepatitis C seropositivity: clinical correlates and effect on early graft and patient survival in adult cadaveric kidney transplantation. J Am Soc Nephrol 2002 Dec;13:2974–82.
[23] Abbott KC, Bucci JR, Matsumoto CS, Swanson SJ, Agodoa LY, Holtzmuller KC, et al. Hepatitis C and renal transplantation in the era of modern immunosuppression. J Am Soc Nephrol 2003 Nov;14:2908–18.
[24] Pecoraro V, Banzi R, Cariani E, Chester J, Villa E, D'Amico R, et al. New Direct-Acting Antivirals for the Treatment of Patients With Hepatitis C Virus Infection: A Systematic Review of Randomized Controlled Trials. J Clin Exp Hepatol 2019 Jul-Aug;9:522–38.
[25] Franco A, Moreso F, Merino E, Sancho A, Kanter J, Gimeno A, et al. Renal transplantation from seropositive hepatitis C virus donors to seronegative recipients in Spain: a prospective study. Transpl Int 2019 Jul;32:710–6.
[26] Blumberg EA. Organs from Hepatitis C Virus-Positive Donors. N Engl J Med 2019 Apr 25;380:1669–70.
[27] Burton JR,Jr, Terrault NA, Goldberg DS, Bloom RD, Gilroy R, Heimbach JK, et al. Liver and Kidney Recipient Selection of HCV-Viremic Donors - Meeting Consensus Report from the 2019 Controversies in Transplantation. Transplantation 2019 Oct 18.
[28] Morales JM, Fabrizi F. Hepatitis C and its impact on renal transplantation. Nat Rev Nephrol 2015 Mar;11:172–82.
[29] Veroux M, Corona D, Sinagra N, Giaquinta A, Zerbo D, Ekser B, et al. Kidney transplantation from donors with hepatitis C infection. World J Gastroenterol 2014 Mar 21;20:2801–9.
[30] Woolley A, Singh S, Goldberg H, Mallidi H, Givertz M, Mehra M. Heart and Lung Transplants from HCV-Infected Donors to Uninfected Recipients. N Engl J Med 2019 Apr;380:1606–17.
[31] Van Handel MM, Rose CE, Hallisey EJ, Kolling JL, Zibbell JE, Lewis B, et al. County-Level Vulnerability Assessment for Rapid Dissemination of HIV or HCV Infections Among Persons Who Inject Drugs, United States. J Acquir Immune Defic Syndr 2016 Nov 1;73:323–31.

Please cite this article as: R.C. van Riet, K.M. van Dijk and M.W.F. van den Hoogen, New possibilities on transplanting kidneys from hepatitis C virus positive donors: a Systematic Revi..., Transplantation Reviews, https://doi.org/10.1016/j.trre.2020.100532