ISSN 2220-3230 (online)

World Journal of *Transplantation*

World J Transplant 2018 August 9; 8(4): 84-121

Published by Baishideng Publishing Group Inc

World Journal of Transplantation

Contents

Volume 8 Number 4 August 9, 2018

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NAME OF JOURNAL
World Journal of Transplantation

ISSN
ISSN 2220-3230 (online)

LAUNCH DATE
December 24, 2011

EDITORIAL OFFICE
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World Journal of Transplantation
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PUBLISHER
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7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
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E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
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PUBLICATION DATE
August 9, 2018

World Journal of Transplantation

Submit a Manuscript: http://www.f6publishing.com

World J Transplant 2018 August 9; 8(4): 84-96

DOI: 10.5500/wjt.v8.i4.84

ISSN 2220-3230 (online)

REVIEW

Hepatitis C and renal transplantation in era of new antiviral agents

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Author contributions: Salvadori M and Tsalouchos A contributed equally to the manuscript; Salvadori M designed the study, performed the last revision and provided answers to the reviewers; Tsalouchos A collected the data from literature; Salvadori M and Tsalouchos A analyzed the collected data and wrote the manuscript.

Conflict-of-interest statement: Maurizio Salvadori and Aris Tsalouchos do not have any conflict of interest in relation to the manuscript.

Manuscript source: Invited manuscript

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Received: February 28, 2018
Peer-review started: March 1, 2018
First decision: March 29, 2018
Revised: April 17, 2018
Accepted: May 30, 2018
Article in press: May 30, 2018

Published online: August 9, 2018

Abstract

Data from World Health Organization estimates that the hepatitis C virus (HCV) prevalence is 3% and approximately 71 million persons are infected worldwide. HCV infection is particularly frequent among patients affected by renal diseases and among those in dialysis treatment. In addition to produce a higher rate of any cause of death, HCV in renal patients and in renal transplanted patients produce a deterioration of liver disease and is a recognized cause of transplant glomerulopathy, new onset diabetes mellitus and lymphoproliferative disorders. Treatment of HCV infection with interferon alpha and/or ribavirin had a poor efficacy. The treatment was toxic, expensive and with limited efficacy. In the post-transplant period was also cause of severe humoral rejection. In this review we have highlighted the new direct antiviral agents that have revolutionized the treatment of HCV both in the general population and in the renal patients. Patients on dialysis or with low glomerular filtration rate were particularly resistant to the old therapies, while the direct antiviral agents allowed achieving a sustained viral response in 90%-100% of patients with a short period of treatment. This fact to date allows HCV patients to enter the waiting list for transplantation easier than before. These new agents may be also used in renal transplant patients HCV-positive without relevant clinical risks and achieving a sustained viral response in almost all patients. New drug appears in the pipeline with increased profile of efficacy and safety. These drugs are now the object of several phases Ⅱ, Ⅲ clinical trials.

Key words: Hepatitis C virus; Renal transplantation; Hepatitis C virus and renal diseases; Interferon based therapies; Direct antiviral agents; Hepatitis C virus-positive donors

Core tip: The prevalence of hepatitis C virus (HCV) infection is high in patients with end-stage renal disease and HCV has clinical challenges in patients who undergo kidney transplantation. Historically, interferon-based treatment options have been limited by low rates of efficacy and significant side effects, including risk of precipitating rejection. Direct acting antiviral (DAA) drugs revolutionized the treatment of HCV. In this review we highlighted the most recent studies and clinical trial with DAA in renal patients including patients waiting for transplantation and already transplanted. In these studies all-oral DAA therapy appears to be safe and effective for such patients.

Salvadori M, Tsalouchos A. Hepatitis C and renal transplantation in era of new antiviral agents. *World J Transplant* 2018; 8(4): 84-96 Available from: URL: http://www.wjgnet.com/2220-3230/full/v8/i4/84.htm DOI: http://dx.doi.org/10.5500/wjt.v8.i4.84

HEPATITIS C VIRUS EPIDEMIOLOGY

The World Health Organization (WHO) estimates that the global prevalence of hepatitis C virus (HCV) infection averages 3%, and the incidence is 3-4 millions of new infections every year[1]. HCV prevalence is not similar worldwide and ranges from less than 0.1% in Northern Europe to 1%-5% in other countries, such as Eastern Europe and the Indian subcontinent[2], to 25% in Egypt[2]. HCV infection is considered to be an endemic disease in some country as Taiwan[3].

HCV prevalence is increasing annually and the October 2017 report from the WHO revealed that 71 million of people are infected worldwide. However, some population-based studies[4-6] have demonstrated that prevalence estimates based on blood donors, underestimate the true HCV prevalence in the general population.

HCV AND RENAL DISEASE

HCV prevalence increases in patients with kidney diseases. HCV may cause chronic kidney disease (CKD) *via* some forms of glomerulonephritis (GN), primarily membranoproliferative GN (MPGN), which may be caused by mixed cryoglobulinemia that represents HCV/anti-HCV immune complex associated with rheumatoid factor and complement[7]. Epidemiological studies in the United States (NHANES Ⅲ) and Taiwan have recently demonstrated the relationship between HCV infection and CKD[8,9].

HCV infection is a frequent consequence of CKD in stages 4-5. Blood transfusions and nosocomial transmission in dialysis units contribute to the much higher prevalence of HCV infection in CKD stage 5 than in the general population. Epidemiological studies documented that HCV infection is associated with a higher risk and shorter time to CKD despite the lower prevalence of many CKD risk factors (ERCHIVES Study)[10]. Another study[11] confirmed that HCV-positive patients exhibit 40% higher odds for renal insufficiency compared with HCV-negative patients after adjustment for age, race, gender, diabetes and hypertension. One retrospective study[12] did not confirm these findings, but the authors recognized the limitation of their study. A relevant longitudinal study including of 23820 adults aged 30-65 years old was performed in Taiwan. The study included 18541 anti-HCV serum-negative patients and 1095 anti-HCV serum-positive patients. The Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer (REVEAL)-HCV study is a large prospective community based cohort study in Taiwan, and long term diseases provide an excellent opportunity to investigate the natural history of chronic hepatitis C and long-term diseases associated with this chronic infection[13]. Lee *et al*[3] documented an association of HCV status and any cause of death. Lai *et al*[14] assessed the risk of developing end-stage renal disease (ESRD) in relation to HCV serostatus, HCV RNA level and HCV genotypes.

The Lai *et al*[14] study documented that chronic HCV infection is an independent risk factor for the development of ESRD. Participants with low and high HCV RNA levels exhibited a 2.6- and a 4.3-fold increased risk of developing ESRD, respectively, compared with participants who were not chronically HCV infected. Patients with HCV genotype 1 exhibit a higher risk of developing ESRD (Figure 1).

CLINICAL PROBLEMS OF HEPATITIS C IN RENAL TRANSPLANT PATIENTS

Survival of HCV-infected patients in ESRD is significantly lower in HCV-positive RNA-positive dialysis patients compared to HCV-positive RNA-positive kidney transplant recipients[15-17]. However, the persistence of HCV infection after renal transplantation is a true risk factor for graft and patient survival. The following complications primarily occur after renal transplantation in HCV-positive patients.

Liver disease

Immunosuppression facilitates HCV replication and accelerates liver disease to result in chronic hepatitis, fibrosing cholestatic hepatitis and rapidly progressive liver failure[18,19]. Therefore, preemptive treatment of HCV infection during dialysis is recommended.

Renal disease

HCV with associated cryoglobulinemia frequently causes MPGN even after renal transplantation[20,21]. Similarly, HCV may cause membranous nephropathy in renal transplant patients[20,22], and it may occur as a recurrent or de novo disease. A higher frequency of acute rejection

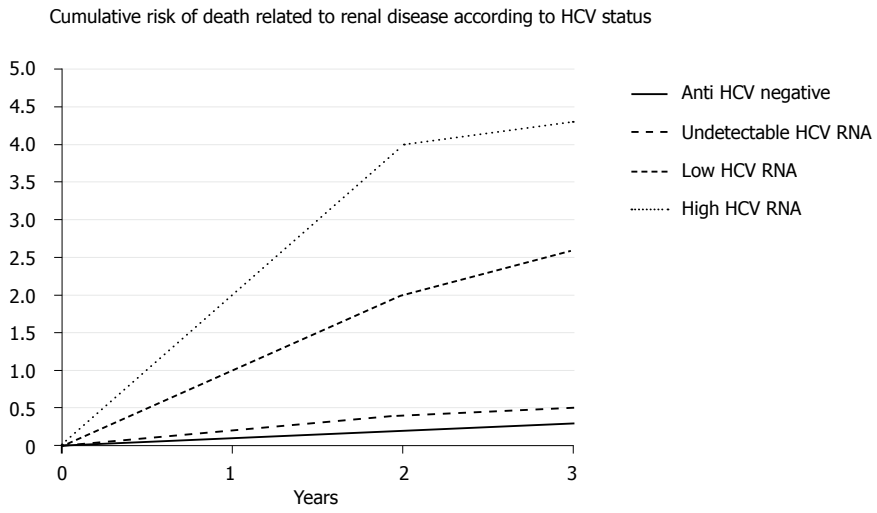

Figure 1 Hepatitis C virus infection is associated with an increased risk of renal disease, end-stage renal disease and renal-related mortality (REVEAL HCV Longitudinal Taiwanese study). HCV: Hepatitis C virus.

was found in HCV-positive patients, but this association is controversial[23,24]. Acute, often humoral, rejection is frequent in the patients receiving interferon (IFN) therapy[25]. Treatment of patients prior to transplantation is necessary, especially when IFN therapy is used. An increased risk of transplant glomerulopathy, the glomerular phenotype of chronic rejection, is associated with HCV infection[26,27]. An increased risk of new onset diabetes mellitus is associated with HCV infection[28,29]. An increase in post-transplant lympho-proliferative disorders was described in HCV patients transplanted with different organs[30].

These findings clearly document the need to manage HCV. The need for treatment during the dialysis period prior to transplantation is also clear. The standard therapy until recently consisted of IFN ± ribavirin administration, but the results were poor with this treatment. IFN was toxic, expensive and exhibited limited efficacy in the pre-transplant period. IFN treatment in the post-transplant period was also dangerous because it caused acute humoral rejections. HCV treatment may be divided in two periods: (1) IFN-based therapies; and (2) Direct acting antiviral (DAA) therapies.

IFN BASED THERAPIES

The first drug used for the treatment of HCV-positive patients with ESRD or transplantation was the recombinant alpha interferon (IFNα) eventually in combination with ribavirin, but the results in terms of sustained viral response (SVR) were poor.

Recombinant IFNα was first used as a monotherapy for chronic hepatitis C, but the drug only produced a modest SVR, several side effects were reported, and treatment was expensive and generated severe acute rejection when used after transplantation[25,31-35]. Fabrizi *et al*[36] performed a meta-analysis and concluded that the efficacy and safety of IFN-based therapies in renal transplant recipients were not satisfactory. The combination of IFNα with ribavirin increased the response rate, but induced the hemolysis as a new dose-dependent side effect[37]. This treatment was the standard of care until 1998. The introduction of pegylated IFNα increased the response rate by an additional 10%[38] and this treatment remained the standard of care until 2011.

The use of antiviral therapy was recommended for HCV patients in renal transplant candidates prior to transplantation because it was safer, effective and sustainable[1]. Several studies[39-44] confirmed these effects, including the Fabrizi *et al*[45] meta-analysis. One large randomized controlled trial recently demonstrated the greater efficacy and safety of combination antiviral therapy (pegylated IFN plus low-dose ribavirin, 200 mg daily) versus monotherapy (pegylated IFN alone) for HCV in a hemodialysis population[46]. The rates of sustained viral response were approximately 70%, and most dialysis patients tolerated the dual therapy well with appropriate patient monitoring.

DAA-BASED THERAPIES

Accumulating evidence and knowledge of the mechanism of action of HCV and the viral proteins involved in its replication during the 2000s allowed for the development of specific drugs for direct antiviral treatment (Figure 2). To date the DAAs may be divided in four classes according the mechanism of action (Table 1)

The first stage of this therapeutic revolution was the therapeutic introduction of protease inhibitors (PIs). The first generation of DAAs was represented by boceprevir and telaprevir, which inhibited NS3/4A protease activity. These drugs are inhibitors and substrates of the cytochrome (CYP) 3A4 isoenzyme in the liver and the intestinal P-glycoprotein (Pgp) transporter. However, these drugs may develop viral resistance. Therefore, these DAAs must be combined with pegylated IFN and

Table 1 The four classes of direct acting antivirals agents

The four classes of DAAs	Mechanism of action	Drugs (targeted genotypes in brackets)
NS3/4A PIs (PIs)	Block a viral enzyme (protease) that enables the HCV to survive and replicate in host cells	Glecaprevir (1-6) Paritaprevir (1, 4) Voxilaprevir (1-6) Grazoprevir (1, 3, 4)
Nucleoside and nucleotide NS5B polymerase inhibitors	Target the HCV to stop it from making copies of itself in the liver. So doing block the virus from multiplying	Sofosbuvir (1-4)
NS5A inhibitors	Block a virus protein, NS5A, that HCV needs to reproduce and for various stages of infection	Ombitasvir (1, 4) Pibrentasvir (1-6) Daclatasvir (3) Elbasvir (1, 4) Ledipasvir (1) Ombitasvir (1) Velpatasvir (1-6)
Non-nucleoside NS5B polymerase inhibitors	Stop HCV from reproducing by inserting themselves into the virus so that other pieces of the HCV cannot attach to it	Dasabuvir (1)

PIs: Protease inhibitors; HCV: Hepatitis C virus.

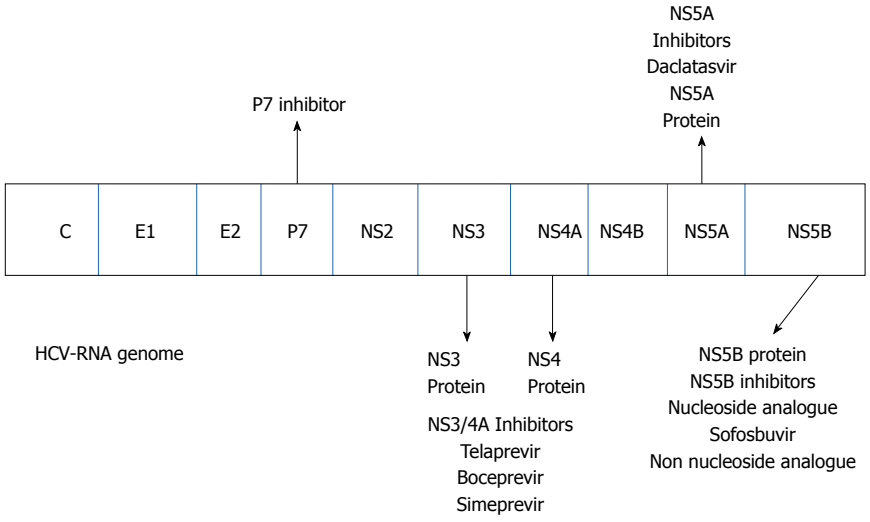

Figure 2 Development of new drugs for hepatitis C virus infection according the hepatitis C virus structure. HCV: Hepatitis C virus.

ribavirin. No dose adjustment is necessary for patients with hepatic or renal impairment[47-50].

New drugs target the 3 non-structural proteins of the NS3 serine protease. These serine PIs include simeprevir, paritaprevir and asunaprevir. Simeprevir is an inhibitor of gut cytochrome 3A4 and organic anion-transporting peptide 1B1/3 (OATP1B1/3), and treatment may produce indirect hyperbilirubinemia. Paritaprevir acts on the same cytochromes as simeprevir. These agents are better tolerated than boceprevir and telaprevir, but the antiviral activity is primarily limited to the HCV genotype Ⅰ. These drugs remain subject to viral resistance and are used in combination with other antiviral drugs. No dose adjustments are necessary in patients with renal impairment[51].

Another group of DAAs are inhibitors of NS5A, such as daclatasvir, ledispasvir and ombitasvir. These drugs inhibit the NS5A protein that controls phosphorilation/hyperphosphorilation and plays a vital role in HCV viral replication. These drugs also exhibit a low barrier of resistance and must be used in combination in combination with others antiviral[51]. No dose adjustments are necessary in patients with CKD.

The newest DAAs include the NS5B inhibitors. These agents are divided into two classes: Nucleoside and non-nucleoside inhibitors. Non-nucleoside inhibitors are less potent, produce viral resistance and are less frequently used[51]. The most important nucleoside NS5B inhibitor is sofosbuvir, which was recently approved for use in combination with other DAAs. Sofosbuvir targets HCV RNA synthesis at the catalytic site of the NS5B enzyme. Incorporation into the new RNA by the polymerase leads to premature chain termination. Numerous IFN-free regimens are in phase 2 and phase 3 clinical trials and

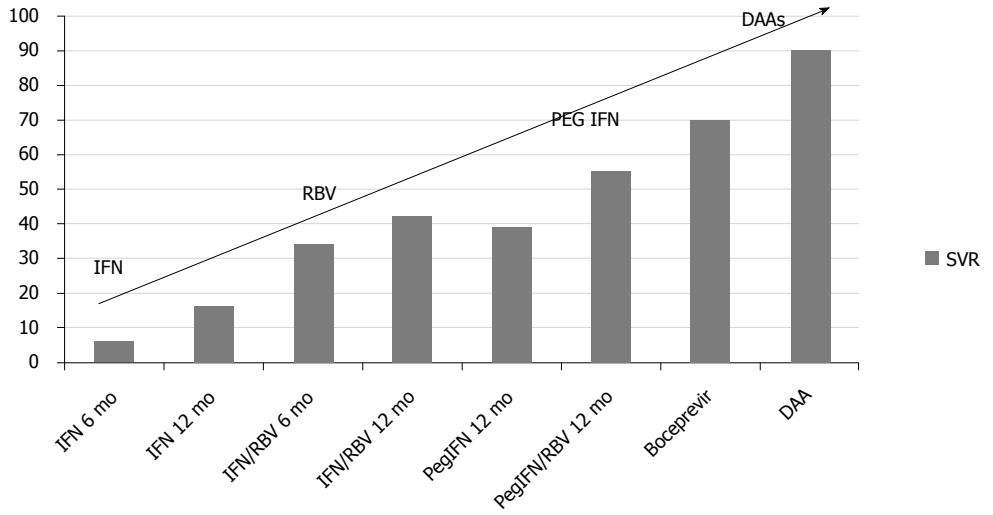

Figure 3 Sustained virological response with different therapies for hepatitis C virus genotype 1. HCV: Hepatitis C virus; SVR: Sustained virological response; IFN: Interferon; PEG IFN: Pegylated IFN; DAA: Direct acting antiviral; RBV: Ribavirin.

these combination regimens attained SVR in 90%-95% of patients[52-54]. Two publications summarize these drugs[55,56]. Figure 3 illustrates SVR improvement over time with different therapies for HCV genotype 1. These data refer to the general population.

EFFECTS OF DAAs IN PATIENTS WITH ESRD AND ON WAITING LISTS FOR RENAL TRANSPLANTATION

The prevalence of HCV infection in dialysis patients and patients on waiting lists for renal transplantation is high, between 6% and 40% and varies geographically[57,58]. In the Dialysis Outcomes Practice Patterns Study (DOPPS) the seroprevalence of HCV infection varies from 20% to 50% according the length on dialysis[59].

Patients with kidney disease are difficult to treat because they present with a high rate of co-morbid conditions, such as hypertension, diabetes mellitus and cardiovascular disease. Co-morbidities facilitate several adverse effects. Few data exist on the pharmacokinetics of DAAs in patients with reduced glomerular filtration rate (GFR). Drug-drug interactions between DAAs and drugs used for lipid-lowering and cardiovascular disease were reported[60]. Table 2 lists the currently available approved DAA-based regimens for the treatment of HCV in patients with renal failure based on HCV genotype[61].

The first-wave DAAs (*e.g.,* boceprevir and telaprevir) exhibited poor efficacy and few patients were treated with these agents. SVR was less than 70% and combination with IFN and ribavirin was mandatory because of viral resistance. Pockros *et al*[62] demonstrated that the combination of ombitasvir, paritaprevir and ritonavir produced SVR in 90% of patients with genotype 1 and stage 4/5 CKD. The regimen was well tolerated, and only the addition of ribavirin produced anemia (Study RUBY I NCT02207088). A more recent study[63] treated 104 patients with CKD and HCV genotypes 1, 2, 3, 4, 5 or 6 with the combination of the NS3/4A protease inhibitor glecaprevir and the NS5A inhibitor pibrentasvir for 3 mo. SVR was obtained in 98% of patients with few adverse events primarily consisting of pruritus, fatigue and nausea (NCT 02651194).

The C-SURFER study (NCT02092350) is a phase 3 study of the administration of NS3/4A protease inhibitor granzoprevir (100 mg) and the NS5A inhibitor elbasvir (50 mg) to 111 patients for 12 wk. The control group received placebo. SVR was obtained in 94.3% of patients, and only 4% of patients reported adverse events, which consisted of headache, nausea and fatigue[64,65]. The recent approval of the first pangenotypic NS5B inhibitor, sofosbuvir, revolutionized the treatment of HCV infection.

Sofosbuvir is a uridine nucleotide analog that inhibits hepatitis C RNA-dependent RNA polymerase and it is effective in all hepatitis C genotypes. Phase Ⅱ and phase Ⅲ studies reported that genotype Ⅰ patients who received sofosbuvir in combination with other DAAs achieved a sustained virological response rate greater than 90%. Different drug associations with sofosbuvir are suggested based on the HCV genotype[66]. Several studies demonstrated the efficacy and safety of these associations[67,68]. Some of these associations are principally useful in particular conditions. For example the association of sofosbuvir and velapatasvir revealed to be efficient in the case of HCV genotype 1, 2 and 3[69] and as rescue therapy in patients who developed viral resistance[53]. Many of these studies were performed in the context of the HCV-TARGET study.

HCV-TARGET is an observational longitudinal survey of patients affected by HCV different genotypes with different levels of renal function. The study is performed

Table 2 Available, approved direct acting antiviral-based regimens for treating hepatitis C virus in treatment-naive patients

Genotype 1a	Genotype 4
Ledipasvir + sofosbuvir	Ledipasvir + sofosbuvir
Paritaprevir + ritonavir + ombitasvir + dasabuvir	Paritaprevir + ritonavir + ombitasvir + dasabuvir + ribavirin
Sofosbuvir+ simeprevir ± ribavirin	Sofosbuvir + ribavirin + pegIFN
	Sofosbuvir + simeprevir + ribavirin
Genotype 1b	**Genotype 5**
Ledipasvir + sofosbuvir	Sofosbuvir + ribavirin
Paritaprevir + ritonavir + ombitasvir + dasabuvir	PegIFN + ribavirin
Sofosbuvir + simeprevir	
Genotype 2	**Genotype 6**
Sofosbuvir + ribavirin	Ledipasvir + sofosbuvir
	Sofosbuvir + ribavirin + pegIFN
Genotype 3	**Pangenotype**
Sofosbuvir + ribavirin	Glecaprevir + pibrentasvir
Sofosbuvir + ribavirin + pegIFN	Sofosbuvir + velatapasvir

pegIFN: Pegylated interferon.

at academic and community medical centers in North America and Europe. The study evaluates the efficacy and safety of antiviral regimens, including sofosbuvir, in 1893 patients (NCT01474811).

Sofosbuvir use was restricted to patients with an eGFR > 30 mL/min, and a few studies investigated the use of sofosbuvir in patients with ESRD[70-73]. Recently, the combination of sofosbuvir plus simeprevir was administered to 17 patients with ESRD. The SVR was 100% after 12 wk treatment. Few patients reported minor or mild adverse events[70].

Rostaing *et al*[74] recently reviewed the treatment of HCV infection in kidney transplant candidates with poor renal function or on dialysis. Saxena *et al*[75] reported the efficacy of sofosbuvir in association with ribavirin in 73 patients with an eGFR < 45 mL/min, and SVR was achieved in 83% of patients. However, these patients exhibited higher rates of anemia and deterioration of renal function regardless of the use of ribavirin. Because of this fact and because of pharmacokinetic studies, sofosbuvir should be administered with extreme caution to patients with reduced GFR. Indeed, the use of sofosbuvir in patients with renal impairment causes an increase in serum levels of sofosbuvir and an increase of the AUC of 171%. Desnoyer *et al*[76] performed a pharmacokinetic study in hemodialysis patients receiving two different doses of sofosbuvir and demonstrated that sofosbuvir did not accumulate in either regimen. Beinhardt *et al*[77] treated 25 patients (10 on dialysis and 15 had received renal or combined liver-renal transplantation with sofosbuvir in association with other DAAs. SVR was obtained in 96% of patients after 12 and 24 wk of treatment, but the treatment response was slower in hemodialysis patients[77]. Alternative treatments for patients with ESRD were reported recently from Japan, where the combined use of daclatasvir plus asunepevir in genotype I dialysis patients achieved a very high SVR rate[78-80].

EFFECTS OF DAAs ON KIDNEY TRANSPLANT PATIENTS WITH HCV INFECTION

We highlighted that the treatment of HCV renal transplant patients in the IFNα era was dangerous, poorly effective and frequently produced acute humoral rejection. Several recent studies demonstrated that the HCV infection eradication was feasible in renal transplant patients using DDAs, with few treatment-related side effects. However, these studies are recent, and the first guidelines for the use of DDAs in renal transplant patients were published at the end of 2017.

Colombo *et al*[81] performed a recent phase 2, open-label clinical trial to evaluate the safety and efficacy of the combination of ledipasvir and sofosbuvir in 5 European centers in 114 renal transplant patients infected with chronic genotype 1 or 4 HCV (NCT 02251717). The authors obtained SVR in 100% of patients after 12 wk of treatment. The eGFR remained stable, and adverse events were common (64%) and included headache, asthenia and fatigue. In one center the association of amiodarone and sofosbuvir probably caused a bradyarrhithmia and the patient interrupted the treatment[82]. The authors concluded that treatment with ledipasvir-sofosbuvir for 12 wk was well tolerated and achieved SVR in 12 wk with an acceptable safety profile. Sawinski *et al*[83] treated 20 renal transplant patients with HCV infection with a sofosbuvir-based therapy. SVR was obtained in all patients at 12 wk. Renal function remained stable, and no rejection occurred. However, 45% of patients required a dose reduction of the calcineurin inhibitor while receiving treatment. Saxena *et al*[84] reported the efficacy of DDAs therapy in 443 patients who received kidney (60) or liver transplant (347) or combined liver-kidney transplantation (36). The study was performed in the context of the vast HCV-TARGET study. Most patients had

HCV genotype Ⅰ. Patients were treated with sofosbuvir/ledipasvir ± ribavirin (85%), sofosbuvir plus daclatasvir ± ribavirin (9%) and ombitasvir/paritaprevir plus dasabuvir ± ribavirin (6%). SVR was achieved in 95.9% of patients after 12 wk of treatment. Six episodes of acute rejection occurred during HCV treatment. The authors concluded that different combinations of DAAs were effective and safe in kidney and/or liver transplant patients. Ribavirin did not influence SVR, and graft rejections were rare. Kamar *et al*[85] demonstrated the efficacy and safety of sofosbuvir-based antiviral therapy for HCV infection after renal transplantation in 25 patients. HCV RNA was not detectable in any patient 12 wk after completing DAA therapy. Treatment was well tolerated without graft rejections or reductions in renal function. Kamar did not observe any drug interaction with calcineurin inhibitors. These data differ from the findings of most studies. Hussein *et al*[86] reported the successful treatment of HCV genotype 4 in 3 renal transplant patients using the combination of sofosbuvir and ribavirin. Fernández *et al*[87] recently published data of the HepaC, which is a Spanish registry of 103 patients treated with DAAs after kidney transplantation. Most patients received a combination of sofosbuvir/ledipasvir or sofosbuvir/daclatasvir. The SVR at 12 wk was 98%. Three episodes of acute humoral rejection occurred, but there were no statistically significant differences in serum creatinine, eGFR or proteinuria before and after treatment. Most patients required immunosuppression dose adjustment, and 36% of patients, mostly cirrhotic, experienced renal dysfunction during antiviral treatment. The authors concluded that a close follow-up is required during treatment because of adjustments in immunosuppression therapy.

The phase 3, open-label, single-arm MAGELLAN-2 study evaluated a 12-wk course of the combination of the pangenotypic NS3/4A inhibitor glecaprevir and the pangenotypic NS5A inhibitor pibrentasvir in liver or renal transplant patients with chronic HCV genotype 1-6. Previous studies demonstrated that all these drugs exhibited a high barrier to resistance, sufficient potency against common NS3 and NS5A polymorphisms and synergistic antiviral activity. The study involved 80 liver transplant patients and 20 kidney transplant patients. The study demonstrated that the treatment with this combination for 12 weeks achieved a 99% SVR in patients with HCV genotypes 1-6. The treatment was well tolerated with few adverse events and confirmed the results obtained by Gane *et al*[63] in patients with ESRD. This new association represents an important alternative in treatment HCV patients after transplantation[88].

The American Association for the Study of Liver Diseases (AASLD) published the following HCV guidelines for kidney transplant patients in 2017[89] (Table 3): (1) The recommended drug association for the treatment of naïve and experienced kidney transplant patients with a genotype 1 or 4 infection: Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for 12 wk. An alternative is a daily fixed-dose combination of ledipasvir (90 mg) and sofosbuvir (400 mg) for 12 wk; and (2) The recommended association for the treatment of naïve and experienced kidney transplant patients with HCV genotypes 2, 3, 5 and 6: Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for 12 wk. An alternative is daily daclatasvir (60 mg) plus sofosbuvir (400 mg) and a low initial dose of ribavirin for 12 wk.

Pharmacokinetic warning for transplant patients

The most important factor to be considered in the treatment of HCV-infected renal transplant patients with DAAs is the possible interactions between DAAs and immunosuppressants. Kwo *et al*[90] recently reviewed this issue and found the following results: Sofosbuvir may be administered to transplant patients without any expected interaction with calcineurin inhibitors. A recent report[91] demonstrated no interaction with mycophenolate mofetil, prednisone or azathioprine. The combination of sofosbuvir and ledipasvir did not reveal any significant interaction with calcineurine inhibitors. No data on possible interactions with sirolimus or everolimus are available. The NS34A protease inhibitor simeprevir did not interact with tacrolimus (TAC), but recent pharmacokinetic studies demonstrated a 5.81-fold increase in the simeprevir AUC levels when administered with cyclosporine (CsA). Therefore, simeprevir should not be administered with CsA. A pharmacokinetic analysis was performed in patients receiving the combination of paritaprevir, ombitasvir and dasabuvir with TAC[92]. There was a 57-fold increase in the TAC AUC, and modeling suggested 0.5 mg of TAC every 7 d with strict monitoring of the TAC levels. A 5.8-fold increase in the CsA AUC was similarly observed, and CsA should be reduced to 1/5. No interaction data are available for paritaprevir, ombitasvir and dasabuvir with sirolimus and everolimus, and the co administration is not recommended. The NS5A inhibitor daclatasvir does not affect the CsA or TAC levels and no dose adjustment is required. The combination of elbasvir and grazoprevir produced a 15-fold increase in the grazoprevir AUC when administered with CsA, and this association is not recommended[89]. The combination of glecaprevir and pibrentasvir with CsA produced a 5-fold increase in the glecaprevir AUC when high doses of CsA were used. This same drug combination with TAC produced a 1.45-fold increase in the TAC AUC, and careful monitoring of the TAC levels is required[89]. Fernández-Ruiz *et al*[93] recently examined eGFR and 24-h proteinuria in 49 renal transplant patients who received sofosbuvir and ledipasvir for 12 mo after treatment. The TAC levels were higher at 12 mo compared to the end of treatment, and the eGFR was significantly decreased. The authors suggested adjusting immunosuppressants when DAAs are administered. Drug monitoring should also be performed after the end of the HCV treatment as well as monitoring of the renal

Table 3 Recommended regimens for kidney transplant patients

Recommended	Duration	Rating
Recommended regimens listed by evidence level and alphabetically for treatment-naive and experienced kidney transplant patients with genotype 1 or 4 infection, with or without compensated cirrhosis		
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)	12 wk	Ⅰ, A[1] Ⅱa, C[2]
Daily fixed dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 wk	Ⅰ, A
Recommended and alternative regimens for treatment-naïve and experienced kidney transplant patients with genotype 2, 3, 4, 5 or 6 infection, with or without compensated cirrhosis		
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)	12 wk	Ⅰ, A[3] Ⅱa, C[4]
Alternative		
Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) plus low initial dose of ribavirin (600 mg; increased as tolerated)	12 wk	Ⅱ, A

[1]Patients without cirrhosis; [2]Patients with compensated cirrhosis; [3]Genotypes 2, 3 and 6; [4]Genotype 5.

function.

TRANSPLANTING KIDNEYS FROM HCV POSITIVE DONORS INTO HCV POSITIVE RECIPIENTS

In the pre DAAs era, because of organ shortage, several transplant centers transplanted kidneys from HCV positive donors into HCV positive recipients. The issue was controversial. One of the largest reports using such strategy is the study of Morales *et al*[94]. In this study 162 HCV positive recipients received a kidney from HCV positive donors and were compared with 306 HCV positive recipients who received kidney from HCV negative donors. The 5 and 10 year patients survival was similar as well as the 5 and 10 years graft survival. The outcomes of the liver disease were also similar in both groups and the Cox regression analysis could not identify the donor's HCV serology as a significant risk factor. These data strongly suggest the use of kidneys from HCV positive donors in HCV positive recipients. Accordingly, the Kidney Disease Improving Global Outcomes (Kdigo)[1] recommended that transplantation of kidneys from HCV RNA positive donors should be directed to the HCV positive recipients. In United States, currently patients with untreated hepatitis C, who accept organ from HCV positive donors, may have a shorter time on transplant waiting list, while in other continents as Europe the positions differ according the different national programs. As afore mentioned direct-acting antiviral has revolutionized the treatment of hepatitis C infection also with implications for the use of HCV vermeil donors. Two recent papers reported the safety of transplanting kidneys from HCV positive donors to HCV positive recipients using DAAs[95,96]. The recommendation is to initiate early post-transplantation a pan-genotype therapy. A sustained SVR was near 100% and the DAA treatment after surgery was 125 d. Looking forward, the American Society of Transplantation (AST) held a consensus conference on the use of HCV viremic donors in solid organ transplantation[97].

The consensus conclusions established that: The term "HCV viremic donors" should be adopted; The provision of DAA to allow transplantation of HCV viremic donors into negative recipients is justified; The transplantation of organs from HCV viremic donors into HCV-negative recipients should be conducted only under monitored protocols and studies; There is a need for well-designed clinical trials of adequate power with conclusive findings to justify payer coverage of DAAs medications.

In this context the trial Exploring Renal Transplants Using Hepatitis C Infected Donors for HCV-negative Recipients (EXPANDER 1)[98] was started at the Johns Hopkins University. If the donor had genotype 1, the treatment included Grazoprevir and Elbasvir started immediately after transplantation and continued for 12 weeks. If the donor had genotype 1 with resistance variants, ribavirin was added. If the donor had genotype 2 or 3, sofosbuvir will be added. The data of this pilot study has been presented at the American Transplant Congress (ATC) 2017. Eight patients have been treated. After treatment no recipient had HCV-RNA detected and no graft failure was observed[99].

CONCLUSION

There has been a revolution in the treatment of chronic hepatitis C. Several oral regimens combining direct-acting antivirals (DAAs) from different families (NS5B nucleotide inhibitors, NS5B non-nucleoside inhibitors, NS5A replication complex inhibitors and NS3/4A PIs) have been developed. These regimens result in an increase in sustained virological response (SVR) rates to above 90% and reduce the duration of treatment to 12 wk or less. As of 2017 several regimens will be approved with additive potencies, without cross-resistance and with a good safety profile. Remaining issues will include increasing screening and access to care so that HCV may become the first chronic viral infection eradicated

Table 4 Main literature studies with direct acting antiviral therapy in patients with chronic hepatitis C and renal dysfunction

Ref.	Title	Journal	Year
[62]	Efficacy of direct-acting antiviral combination for patients with HCV genotype 1 infection and severe renal impairment or end-stage renal disease	*Gastroenterology*	2016
[63]	Glecaprevir and Pibrentasvir in patients with HCV and severe renal impairment	*N Engl J Med*	2017
[64]	Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with HCV genotype 1 infection and stage 4-5 chronic kidney disease (the C-SURFER study): A combination phase 3 study	*Lancet*	2015
[65]	Elbasvir plus grazoprevir in patients with HCV infection and stage 4-5 chronic kidney disease: clinical, virological, and health-related quality-of-life outcomes from a phase 3, multicentre, randomized, double-blind, placebo-controlled trial	*Lancet Gastroenterol Hepatol*	2017
[70]	Use of sofosbuvir-based direct-acting antiviral therapy for HCV infection in patients with severe renal insufficiency	*Infect Dis*	2015
[71]	Safety, efficacy and tolerability of half-dose sofosbuvir plus simeprevir in treatment of hepatitis C in patients with end stage renal disease	*J Hepatol*	2015
[72]	Sofosbuvir and simeprevir in hepatitis C genotype 1-patients with end-stage renal disease on haemodialysis or GFR < 30 mL/min	*Liver Int*	2016
[74]	Use of direct-acting agents for HCV-positive kidney transplant candidates and kidney transplant recipients	*Transpl Int*	2016
[75]	Safety and efficacy of sofosbuvir-containing regimens in hepatitis C-infected patients with impaired renal function	*Liver Int*	2016

HCV: Hepatitis C virus.

Table 5 American Association for the Study of Liver Diseases Recommendation for treating hepatitis C virus in patients with renal impairment

Recommended	Rating	Genotype	Duration
Recommendations for patients with CKD stage 1, 2 or 3			
No dose adjustment is required when using			
(1) Daclatasvir (60 mg)			
(2) Daily fixed-dose combination of elbasvir (50 mg)/grazopevir (100 mg)			
(3) Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)			
(4) Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	I , A		
(5) Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)			
(6) Simeprevir (150 mg)			
(7) Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)			
(8) Sofosbuvir (400 mg)			
Recommendations for patients with CKD stage 4 or 5 (eGFR < 30 mL/min or ESRD			
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	I , B	1a, 1b, 4	12 wk
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)	I , B	1, 2, 3, 4, 5, 6	8 to 16 wk

CKD: Chronic kidney disease; ESRD: End-stage renal disease.

Table 6 European Association for the Study of the Liver Recommendations for treating hepatitis C virus in patients with reduced or absent renal function

Hemodialysis patients, particularly those who are suitable candidates for renal transplantation, should be considered for antiviral therapy (B1)
Hemodialysis patients should receive an IFN-free, if possible ribavirin-free regimen, for 12 wk in patients without cirrhosis, for 24 wk in patients with cirrhosis (B1)
Simeprevir, daclatasvir, and the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir are cleared by hepatic metabolism and can be used in patients with severe renal disease (A1)
Sofosbuvir should not be administered to patients with an eGFR < 30 mL/min per 1.73 m^2 or with end-stage renal disease until more data is available (B2)

worldwide.

The efficacy and safety of these new DAAs are primarily important in the field of renal diseases of patients affected by ESRD and of patients in dialysis waiting for a renal transplant and in patients already transplanted, but with HCV infection. The problem of HCV infection was particularly relevant in uremic patients in the pre-DAAs era and HCV was difficult to be eradicated.

The main studies in this field are cited in Table 4. Table 5 and Table 6 shows the recommendations for treating HCV in patients with renal impairment given from the American Association for the study of liver disease (AASLD)[90] and the European Association for the Study of the Liver (EASL)[60]. The access to transplantation to dialysis patients was allowed, but complications after transplantation were frequent and treatment was not possible after transplantation.

DAAs are able to eradicate HCV in dialysis patients with a short course therapy obtaining a SVR close to 100%. Additionally, DAA-treatment is successful even after transplantation. Particular attention must be devolved to the interference between DAAs and calcineurin inhibitors. Either an increase of CsA or TAC AUC or an increase of DAA AUC is possible and monitoring is essential even after long time after transplantation

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P- Reviewer: Cholongitas E, Cheungpasitporn W, Larrubia JR, Zhu X
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Tan WW

World Journal of Transplantation

Submit a Manuscript: http://www.f6publishing.com

World J Transplant 2018 August 9; 8(4): 97-101

DOI: 10.5500/wjt.v8.i4.97

ISSN 2220-3230 (online)

MINIREVIEWS

Review of stem cells as promising therapy for perianal disease in inflammatory bowel disease

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Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Conflict-of-interest statement: No potential conflicts of interest. No financial support.

Manuscript source: Invited manuscript

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Received: March 29, 2018
Peer-review started: March 29, 2018
First decision: April 10, 2018
Revised: April 22, 2018
Accepted: June 8, 2018
Article in press: June 9, 2018
Published online: August 9, 2018

Abstract

Those patients with perianal Crohn's disease or ulcerative colitis experience a difficult to treat disease process with a delayed state and often inability to heal despite current therapies. The approaches currently used to treat these patients with corticosteroids, antibiotics, immunomodulators, anti-tumor necrosis factor-α drug, and surgical repair are limited in their healing ability. This review presents all current literature since emergence in the early 2000s of stem cell therapy for patients with perianal inflammatory bowel disease and analyzes the efficacy, outcomes and safety within these studies.

Key words: Crohn's disease; Stem cells; Mesenchymal; Perianal disease; Fistula; Inflammatory bowel disease

Core tip: Allogeneic and autologous mesenchymal stem cells (MSCs) are being researched for use in patients with refractory perianal Crohn's disease. Studies from 2003 until now demonstrate efficacy and safety of MSC therapy in this patient population. Up until now, there are no large multi-center, randomized double-blind, placebo-controlled studies examining this.

Dailey FE, Turse EP, Naseer M, Bragg JD, Tahan V. Review of stem cells as promising therapy for perianal disease in inflammatory bowel disease. *World J Transplant* 2018; 8(4): 97-101 Available from: URL: http://www.wjgnet.com/2220-3230/full/v8/i4/97.htm DOI: http://dx.doi.org/10.5500/wjt.v8.i4.97

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory condition of the gastrointestinal tract that can disturb anywhere from the mouth to the anus. One of the most common manifestations of CD includes perianal disease, specifically including fistulas, abscesses, fissures, and stenosis. These complications frequently result in a significant burden for the patient due to abscess formation, perianal leakage, pain, and an overall decreased quality of life. Treatment options for perianal CD have traditionally included symptomatic management, antibiotics, and medications including immunomodulators and anti-tumor necrosis factor α agents, or surgery in cases with persistent refractory disease. However, surgical options are often limited and come with their own risks, which include incontinence and recurrence of disease. Recently, however, mesenchymal stem cells (MSCs) have been studied in perianal CD and results have been quite promising. This paper provides an up-to-date review on the use of MSC for perianal CD.

MSC therapy has been demonstrated to be a potentially effective treatment for perianal CD in a variety of ways. These stem cells are non-hematopoietic multipotent cells that can depress immune activation and encourage healing of inflamed tissue. MSCs have been found to hinder dendritic cell formation from monocytes, restrict naïve and memory CD4+ cells, stop T cell activation via inhibitory effects on mature dendritic cells, and encourage proliferation of regulatory T cells[1-6]. In addition, MSCs can travel to the site of inflammation and there contribute to local healing[7]. Over the last several years, multiple studies have evaluated autologous and allogeneic MSCs, to determine the safety and efficacy of treating perianal CD. The results are promising demonstrating significantly increased rates of healing for perianal disease refractory to conventional therapy alone. Here we will present studies involving autologous adipose, then autologous bone marrow studies, and then allogeneic adipose and bone marrow studies.

AUTOLOGOUS ADIPOSE STEM CELL STUDIES

The first report describing MSCs for perianal CD was a case report by García-Olmo *et al*[8] in 2003. Here, a rectovaginal fistula in CD was successfully healed seven days after the injection of adipose-derived MSCs. This same author then executed a phase Ⅰ clinical trial involving four individuals suffering from refractory complex Crohn's fistulas, again injecting the fistula tracts with autologous adipose-derived MSCs. Tissue repair was reported in three of four of patients at eight weeks, without adverse events during the one and two year follow up visits[9].

García-Olmo *et al*[10] then led a third study, a phase IIb trial, involving 49 patients with complex perianal cryptoglandular and CD fistulas comparing fibrin glue therapy to fibrin glue plus adipose-derived MSCs. Individuals in this latter group received a second dose of MSC if fistula healing did not appear after two months. In those with CD, fistula healing at twelve months occurred in five of seven (71%) in those given fibrin glue plus MSC as opposed to one of seven (14%) in those given fibrin glue alone[10]. Quality of life was also found to be better in the combined treatment group[10]. These early positive findings for MSCs treating perianal CD laid the groundwork for further work. In a dose-escalation phase Ⅰ trial led by Cho *et al*[11], ten individuals affected by perianal CD fistulas were given autologous adipose-derived MSCs. Following two months of treatment, fistula healing marked by epithelization was detected in three in ten (30%), with continued results at the eight month visit.

Lee *et al*[12] performed a follow-up phase Ⅱ study, including 33 treated subjects given injections of fibrin glue and adipose-derived MSCs with doses proportionate to fistula sizes, followed by repeat injections of increased doses if fistula closure did not complete by two months. Fistula healing was found in twenty-seven of thirty-three (82%) individuals by two months, with continued healing to twelve months in twenty-three of twenty-six (88%)[12]. The other six subjects of the original group developed an incomplete closure, five of which had a > 50% closure and decreased drainage[12].

Cho *et al*[13] did a further follow up study from their 2013 phase Ⅰ trial. Here adipose-derived MSC in fistulizing CD analyzed forty-one of forty-three patients for 12 mo and 24 mo weeks showing complete healing in 80.8% (21 of 26) patients in the complete healing pool and 75% (27 of 36) patients in the modified intention to treat pool[13]. The modified intention to treat pool included those patients who had efficacy data at one year in the phase Ⅱ study. Interestingly, regarding maintenance of complete closure, 27 patients achieved this at eight weeks, twenty-three of 26 (88.5%) at twelve months, twenty of 24 (83.3%) at twenty-four months[13]. Recurrence was seen in 11.5% at one year and 16.7% at two years. For the modified intention to treat group nine patients (25%) demonstrated an incomplete response at two years. Thus, the authors concluded that the use of MSC is safe and efficacious in perianal fistulizing disease.

For the Cho *et al*[13] study, one of the most unique aspects is the analysis of patients with MSC therapy and anti-TNF therapy. Of the twenty-four month group of twenty-seven patients showing complete healing, four patients receiving infliximab were documented. This was used due to enteric CD exacerbation, with 75% of these patients having complete closure prior to treatment with infliximab and having continued resolution of their fistula after infusion.

More recently, Dietz *et al*[14] led a phase Ⅰ clinical trial over a six month period assessing the safety and feasibility of autologous stem cell therapy for persistent,

Table 1 Summary of studies utilizing stem cell therapy in perianal Crohn's disease

Ref.	Study year	Stem cell therapy type	Type of study	Type of perianal disease	Method and amount of administration	Concurrent therapies	Outcome
[8]	2003	Autologous Adipose Stem Cell Studies	Case Report	Complex recurrent rectovaginal CD fistula	Local injection of 9 × 106 MSCs	Olsalazine (previously failed immunomodulators and biologics)	Healed 7 d after injection; no serious adverse events from MSC therapy were observed
[9]	2005	Autologous Adipose Stem Cell Studies	Phase Ⅰ Clinical Trial	Complex refractory CD fistulas, refractory to medical therapy and failing surgical therapy at least twice	Local injection of 3 × 106 MSCs	Immunosuppression without infliximab	Tissue repair in 75% (3 of 4) patients at 8 wk, no AE at 1 and 2 yr follow up; no serious adverse events from MSC therapy were observed
[10]	2009	Autologous Adipose Stem Cell Studies	Phase IIb Clinical Trial	Complex perianal cryptoglandular and CD fistulas, refractory to medical and surgical therapy (including at least one induction with anti-TNF)	Local injection of 2 × 106 MSCs plus fibrin glue vs fibrin glue alone; second local injection of 4 × 106 MSCs if no healing seen at 8 wk	Immunosuppression without infliximab, cyclosporine, or tacrolimus	71% (5 of 7) with fistula healing at 12 mo *vs* 14% healing in control group; higher quality of life in those with stem cell treatment; 1 serious adverse event from therapy (anal abscess)
[11]	2013	Autologous Adipose Stem Cell Studies	Dose-escalation Phase Ⅰ Clinical Trial	Perianal CD fistula, with CD confirmed by biopsy; 5 patients with previously unsuccessful surgical therapy	Local injection of 1 × 107, 2 × 107, 4 × 107 MSC, based on fistula size (total of 3-40 × 107 MSC)	Immunosuppression including infliximab	30% (3 of 10) patients with complete healing at two months and then continued eight month follow up; no serious adverse events from MSC therapy were observed
[12]	2013	Autologous Adipose Stem Cell Studies	Dose-proportional Phase Ⅱ Clinical Trial	Perianal CD fistula, less than 2cm in length	Local injection of 3 × 107 or 6 × 107 MSC, per 1 cm of fistula length; average 15.8 × 107 MSC, followed by second injection of 1.5 × previous (average 19 × 107 MSC) if incomplete closure at 8 wk	Immunosuppression including infliximab, but no infliximab within three months prior to MSC therapy	82% (27 of 33) patients with healing at 2 mo and continued healing of 88% these individuals (23 of 26) at 12 mo; of the 6/33 patients with incomplete closure, 5 had > 50% closure; no serious adverse events from MSC therapy were observed
[13]	2015	Autologous Adipose Stem Cell Studies	Phase Ⅱ Clinical Trial	Perianal CD fistulas	Local injection of 3 × 107 MSC, per 1 cm of fistula length; if second dose needed, 1.5 × previous dose administered	Immunosuppression including biologics	80.8% (21 of 26) patients with complete healing at 12 and 24 mo; recurrence in 11.5% at 12 mo and 16.7% at 24 mo; no serious adverse events from MSC therapy were observed
[14]	2017	Autologous Adipose Stem Cell Studies	Phase Ⅰ Clinical Trial	Refractory Perianal Fistulas in CD	Intra-operative placement of fistula plug, consisting of 20 × 106 MSC per plug attached to a bioabsorbable matrix	Biologic therapies (patients had failure to immunomodulators)	Healing in 83% (10 of 12) of patients at 6 mo; no serious adverse events from MSC therapy were observed
[15]	2011	Autologous Bone Marrow Stem Cell Studies	Phase Ⅱ Clinical Trial	Active complex perianal CD fistulas, refractory to medical and surgical therapies (including biologics)	Local injection of 1.5-3 × 107 MSC every 3 wk until improvement or until no longer available (2-5 injections total)	All patients took mesalamine and azathioprine, except for 2 taking prednisone with mesalamine and 2 on mesalamine monotherapy	Complete closure 67% (6 of 9) patients at 2 mo with continued closure at 12 mo; no serious adverse events from MSC therapy were observed

[16]	2017	Allogeneic Adipose Stem Cell Studies	Phase Ⅲ Randomized Clinical Trial	Refractory complex perianal CD fistulas; maximum of 2 internal and 3 external openings; draining for at least 6 wk	Local injection of 120 million C × 601 MSC or placebo; second injection of	Biologic therapies, immunomodulators, antibiotics	Closure at 24 wk in 50% (53 of 107) patients compared to placebo 34% (36 of 105) patients; shorter time to remission in treatment group *vs* placebo: 6.7 wk *vs* 14.6 wk; serious adverse events occurred in 6.8% of treatment subjects (7 of 103) and 6.9% of placebo subjects (7 of 102)-in both groups, the most common serious events were anal abscess/fistula and proctalgia
[17]	2015	Allogeneic Bone Marrow Stem Cell Studies	Phase IIa Randomized Clinical Trial	Refractory perianal CD fistulas to medical and surgical therapies, including all patients refractory to anti-TNF therapy	Local injections of 1 × 107 MSC for 5 patients; 3 × 107 MSC for 5 patients; 9 × 107 MSC for 5 patients; placebo for 6 patients	Stable doses of concurrent therapies, including mesalamine and steroids > 4 wk, immunomodulators > 8 wk, and anti-TNF > 8 wk	Healing in 47% (7 of 15) patients with MSC therapy vs 33% (2 of 6) with placebo at 12 wk; no serious adverse events from MSC therapy were observed

AE: Adverse events; MSC: Mesenchymal stem cell; CD: Crohn's disease; TNF: Tumor necrosis factor.

refractory perianal CD. This trial, dubbed Stem Cells on Matrix Plugs (STOMP), delivered concentrated, adipose-derived MSC attached to a bioabsorbable matrix to 12 patients. By three months, 9 of 12 patients (75%) achieved complete healing through clinical and radiographic determination; by six months, 10 of 12 of patients (83%) achieved this. There were no serious adverse events due to MSC therapy nor plug placement, and the study authors found these matrix plugs to be safe and effective for refractory perianal CD[14].

AUTOLOGOUS BONE MARROW STEM CELL STUDIES

There is much less data available regarding autologous bone marrow MSC treatment, compared to adipose-derived MSC treatment, in CD. A study led by Ciccocioppo utilized nine subjects with actively draining complex perianal fistulas who received intrafistular injections of bone marrow-derived MSC once monthly until healing was achieved or until they were no longer accessible. In all subjects, MSC expansion was successful. The fistulas were wholly closed in six of nine (67%) subjects at two months, with continued results at twelve months; in the other three cases incomplete closure was achieved[15].

ALLOGENEIC ADIPOSE STEM CELL STUDIES

A longer-term study evaluating allogeneic adipose-derived MSC for perianal CD was recently published with encouraging results. Led by Panes, this phase Ⅲ randomized clinical trial included 212 patients across 49 hospitals in Israel and Europe; 107 were given one injection of MSCs and 105 were given placebo with a saline injection. These participants had complex, medically refractory perianal fistulas draining for at least 6 wk, with a maximum of 2 internal and 3 external openings. The patients were kept on concurrent therapy during this study with biologics or immunomodulators or antibiotics. Twenty-four weeks after one local injection, those given MSC had significant clinical improvement delineated by closure of the external fistula tract and no fluid collections > 2 cm on magnetic resonance imaging (MRI). The authors found 53 of 107 subjects (50%) treated with MSC healed as opposed to 36 of 105 subjects (34%) given placebo (n = 36). Additionally, those given MSC experienced a much shorter time to remission of their disease: 6.7 wk as opposed to 14.6 wk. Explanations for why those in the placebo group experienced such high rates of fistula closure and remission include the fact that all patients received fistula curettage, internal orifice closure, and surgical drainage. While this study did not address the potential benefits of repeat injections of MSCs or dosage of injections based on size of fistula tract, it did provide large-scale, sustained positive results of MSCs for perianal CD. An expansion of this project has been developed in the United States, which is also a phase Ⅲ multicenter, randomized clinical trial evaluating allogeneic adipose-derived MSC for perianal CD[16].

ALLOGENEIC BONE MARROW STEM CELL STUDIES

Finally, Molendijk *et al*[17] studied allogeneic MSCs derived from bone marrow in a phase IIa randomized clinical trial in the Netherlands. There were twenty-one patients with refractory perianal fertilizing CD included; five were given a single shot of 1 × 107 MSCs, five were given 3 × 107 MSCs, five were given 9 × 107 MSCs, and six were given placebo. These injections were placed around the internal openings of fistula walls. Fistula healing was determined to be cessation of drainage and absence of fluid collections > 2 cm on MRI, and was observed in

seven of 15 (47%) of those administered MSCs and two of 6 (33%) of those given placebo. These encouraging results were found not only at the study's primary endpoint, week twelve, but also endured through week twenty-four. Amongst the range of dosages of MSCs given, the best effects were observed in those given 3 × 107. Notably, none of the treatment regimens were associated with an increase in adverse events (Table 1)[17].

CONCLUSION

Perianal CD is quite challenging for both patients and providers with delayed and difficult healing, despite current standard therapy including antibiotics, immunomodulators, anti-TNF treatment, and surgical repair. Need for novel treatment options to improve outcomes in these patients is obvious. Here, the promising results of recent and ongoing studies utilizing stem cell therapy-either allogeneic or autologous-for treatment of this patient population are presented. Given this data, the authors conclude that future randomized double-blind, placebo-controlled multi-center studies on the efficacy and safety of stem cell therapy for perianal disease in CD are warranted.

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P- Reviewer: Cheifetz AS, Vasudevan A **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Tan WW

World Journal of Transplantation

Submit a Manuscript: http://www.f6publishing.com

World J Transplant 2018 August 9; 8(4): 102-109

DOI: 10.5500/wjt.v8.i4.102

ISSN 2220-3230 (online)

ORIGINAL ARTICLE

Retrospective Study

Kidney transplantation in older recipients: Preemptive high KDPI kidney *vs* lower KDPI kidney after varying dialysis vintage

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Author contributions: Chopra B participated in literature search, data analysis and manuscript writing; Sureshkumar KK participated in literature search, data analysis and manuscript writing.

Institutional review board statement: The IRB has received this information and finds it qualifies for exempt status according to the following category in the code of regulations: 45 CFR 46.101 (b) Category (4) and with a "Waiver of HIPAA Authorization".

Informed consent statement: Since the data set is de-identified, IRB exempted the study from requiring informed consent.

Conflict-of-interest statement: None.

Manuscript source: Invited manuscript

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Received: April 10, 2018
Peer-review started: April 11, 2018
First decision: May 3, 2018
Revised: May 21, 2018
Accepted: May 30, 2018
Article in press: May 31, 2018
Published online: August 9, 2018

Abstract

AIM

To evaluate the outcomes of transplanting marginal kidneys preemptively compared to better-quality kidneys after varying dialysis vintage in older recipients.

METHODS

Using OPTN/United Network for Organ Sharing database from 2001-2015, we identified deceased donor kidney (DDK) transplant recipients > 60 years of age who either underwent preemptive transplantation of kidneys with kidney donor profile index (KDPI) ⩾ 85% (marginal kidneys) or received kidneys with KDPI of 35%-84% (better quality kidneys that older wait-listed patients would likely receive if waited longer) after being on dialysis for either 1-4 or 4-8 years. Using a multivariate Cox model adjusting for donor, recipient and transplant related factors- overall and death-censored graft failure risks along with patient death risk of preemptive transplant recipients were compared to transplant recipients in the 1-4 and 4-8 year dialysis vintage groups.

RESUTLS

The median follow up for the whole group was 37 mo (interquartile range of 57 mo). A total of 6110 DDK transplant recipients above the age of 60 years identified during the study period were found to be eligible to be included in the analysis. Among these patients

350 received preemptive transplantation of kidneys with KDPI ⩾ 85. The remaining patients underwent transplantation of better quality kidneys with KDPI 35-84% after being on maintenance dialysis for either 1-4 years (n = 3300) or 4-8 years (n = 2460). Adjusted overall graft failure risk and death-censored graft failure risk in preemptive high KDPI kidney recipients were similar when compared to group that received lower KDPI kidney after being on maintenance dialysis for either 1-4 years (HR 1.01, 95%CI: 0.90-1.14, P = 0.84 and HR 0.96, 95%CI: 0.79-1.16, P = 0.66 respectively) or 4-8 years (HR 0.82, 95%CI: 0.63-1.07, P = 0.15 and HR 0.81, 95%CI: 0.52-1.25, P = 0.33 respectively). Adjusted patient death risk in preemptive high KDPI kidney recipients were similar when compared to groups that received lower KDPI kidney after being on maintenance dialysis for 1-4 years (HR 0.99, 95%CI: 0.87-1.12, P = 0.89) but lower compared to patients who were on dialysis for 4-8 years (HR 0.74, 95%CI: 0.56-0.98, P = 0.037).

CONCLUSION

In summary, our study supports accepting a "marginal" quality high KDPI kidney preemptively in older wait-listed patients thus avoiding dialysis exposure.

Key words: Preemptive kidney transplantation; Kidney donor profile index; Dialysis vintage; Kidney transplant outcomes; Older recipients; Waiting list

Core tip: Increasing waiting-time for deceased donor kidney (DDK) transplantation adversely impacts older patients disproportionately. Dialysis vintage and transplantation of "marginal kidneys" are associated with inferior post-transplant outcomes. Using OPTN/United Network for Organ Sharing database from 2001-2015, we compared the outcomes of preemptive transplantation of marginal [kidney donor profile index (KDPI) ⩾ 85%] DDKs compared to transplanting better quality DDKs (KDPI 35%-84%) after being on dialysis for 1-4 and 4-8 years in patient > 60 years old. Preemptive transplantation of marginal kidneys provided non-inferior graft and patient outcomes compared to transplanting better quality kidneys in older patients on maintenance dialysis. Early transplantation could also provide quality of life and cost benefits.

Chopra B, Sureshkumar KK. Kidney transplantation in older recipients: Preemptive high KDPI kidney *vs* lower KDPI kidney after varying dialysis vintage. *World J Transplant* 2018; 8(4): 102-109 Available from: URL: http://www.wjgnet.com/2220-3230/full/v8/i4/102.htm DOI: http://dx.doi.org/10.5500/wjt.v8.i4.102

INTRODUCTION

Number of patients waiting for kidney transplantation has been steadily growing in the United States with nearly 100000 currently on the waiting list. Organ shortage is the major limiting factor. With the intention to optimize utilization of deceased donor kidneys (DDKs), Organ Procurement and Transplant Network (OPTN) implemented the new kidney allocation system (KAS) in December 2014[1]. In the new KAS, each kidney is allocated a kidney donor profile index (KDPI) based on 10 donor variables. KDPI is derived from the prediction model termed kidney donor risk index (KDRI) which was originally proposed by Rao *et al*[2] in 2009. KDPI score ranges from 0%-100% with higher scores meaning lower quality kidneys. For instance, a KDPI score of 85% means that the kidney quality is worse than 85% of kidneys recovered for transplantation during the previous calendar year. The new KAS promotes allocation of better quality kidneys to recipients with better estimated post-transplant survival in a concept called longevity matching[3]. On the other hand, kidneys with higher KDPI are likely offered to older recipients.

Preemptive transplantation (transplantation before the need for maintenance dialysis) has been shown to be associated with better post-transplant outcomes[4,5]. Dialysis vintage is an independent predictor of adverse long-term outcomes following both deceased and living donor kidney transplantation[6-9]. Kidneys with KDPI ⩾ 85% are considered "marginal" and transplantation of such organs are associated with inferior outcomes when compared to transplanting kidneys with lower KDPI[10]. It is unclear whether preemptive transplantation of high KDPI kidneys and thus avoiding maintenance dialysis in older recipients would be beneficial compared to waiting for and transplanting lower KDPI kidneys after being on dialysis for varying lengths of time. We sought to answer this by utilizing the national transplant database.

MATERIALS AND METHODS

Study population

The study protocol was approved by the institutional review board and was conducted in accordance with the ethical standards laid down in the 2000 Declaration of Helsinki as well as 2008 Declaration of Istanbul. Using OPTN/United Network for Organ Sharing (UNOS) database, we identified patients older than 60 years who underwent first time DDK transplantation between January 2001 and December 2015, after receiving perioperative antibody induction and discharged on a calcineurin inhibitor (CNI) and Mycophenolate Mofetil (MMF) based maintenance immunosuppression. From this group, we further identified patients who underwent preemptive transplantation with kidneys with KDPI ⩾ 85% and those who underwent transplantation of kidneys with KDPI of 35%-84% after being on maintenance dialysis for either 1-4 years or 4-8 years. We chose KDPI of 35%-84% in the dialysis groups in order to approximate real life scenarios since older patients who wait longer will likely get offer for DDKs with mid-range quality with new KAS. KDPI was calculated retrospectively by OPTN/UNOS and is available in their

Table 1 Demographics

	Preemptive-high KDPI (n = 350)	1-4 yr dialysis vintage-lower KDPI (n = 3300)	Preemptive-high KDPI (n = 350)	4-8 yr dialysis vintage-lower KDPI (n = 2460)
KDPI	93 ± 4	62 ± 14	93 ± 4	62 ± 9
Dialysis duration (mo)	0	31 ± 10	0	67 ± 13
Age (donor)	61 ± 12	46 ± 13[b]	61 ± 12	46 ± 14[b]
Donor gender (M) %	46.8	56[d]	46.8	54.3[a]
DCD kidney (%)	8.6	14.4[d]	8.6	14.9[d]
ECD kidney (%)	89.4	25.6[b]	89.4	26[b]
HLA mismatch	4.5 ± 1.3	3.9 ± 1.7[b]	4.5 ± 1.3	4.3 ± 1.4[a]
Recipient age (years ± SD)	69 ± 5	67 ± 4[a]	69 ± 5	67 ± 4[b]
Recipient gender (M) %	52.4	63.5[b]	52.4	64[b]
African American Recipient (%)	14.7	20.9[a]	14.7	30.8[b]
Recipient diabetes (%)	30.4	51[b]	30.4	52.5[b]
Recipient BMI (%)	27 ± 4	28 ± 5[a]	27 ± 4	28 ± 5
Calculated PRA	4.6 ± 14	10 ± 25[b]	4.6 ± 14	13 ± 27[b]
Cold ischemia time (h)	19 ± 8	18 ± 9	19 ± 8	18 ± 9
Delayed graft function (%)	5.3	29[b]	5.3	37.5[b]
Depleting induction (%)	65.5	69.8	65.5	71.5[a]
Steroid maintenance (%)	64	69.6[a]	64	70.2[a]
Kidney pumped (%)	53.7	42.2[b]	53.7	44[d]
Transplant year	2009 ± 4	2008 ± 4[a]	2009 ± 4	2010 ± 3[b]

[a]$P \leqslant 0.05$, [b]$P \leqslant 0.001$, [d]$P \leqslant 0.005$, *vs* preemptive-high KDPI kidneys. BMI: Body mass index; DCD: Donation after cardiac death; ECD: Expanded criteria donor; HLA: Human leukocyte antigen; KDPI: Kidney donor profile index; PRA: Panel reactive antibody.

database. Patients were excluded from the analysis if they received previous transplant, underwent live donor kidney, or multi-organ transplantation. Patients were also excluded if they received no induction or were on maintenance regimen other than CNI/MMF.

Demographic variables for the three groups were collected. Overall and death-censored graft failure risks along with patient death risk associated with preemptive transplantation of high KDPI ($\geqslant$ 85%) kidneys were compared to these outcomes associated with transplantation of lower KDPI (35%-84%) kidneys among recipients who were on maintenance dialysis for 1-4 years and 4-8 years after correcting for pre-specified variables. The covariates used for correction in the multivariate model were: donor related including age, gender, expanded criteria donor kidney, donation after cardiac death kidney, cause of donor death; recipient related including age, African American race, diabetes mellitus, hepatitis B and C sero-positivity, ESRD cause, dialysis duration, panel reactive antibody (PRA) titer (peak PRA till 2009 and calculated PRA from 2009 onwards), human leukocyte antigen mismatch; transplant related including type of induction, cold ischemia time, pump perfusion of kidney, delayed graft function (defined as need for dialysis within the first week of transplantation), steroid maintenance, and transplant year.

Statistical analysis

Continuous variables were compared between groups using 2-tailed *t*-tests and categorical variables were compared using χ^2 test. Values were expressed as either mean ± standard deviation or as percentages. Missing values were addressed by imputing means of the variables. Cox model was used to compare adjusted graft and patient outcomes between the groups. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated. A P value of < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS software version 18 (IBM, Armonk, NY, United States).

RESULTS

Demographic characteristics

The median follow up for the whole group was 37 mo (interquartile range of 57 mo). A total of 6110 DDK transplant recipients above the age of 60 years identified during the study period were found to be eligible to be included in the analysis. Among these patients 350 received preemptive transplantation of kidneys with KDPI $\geqslant$ 85. The remaining patients underwent transplantation of better quality kidneys with KDPI 35%-84% after being on maintenance dialysis for either 1-4 years (n = 3300) or 4-8 years (n = 2460).

The demographic features of the different groups are shown in Table 1. Preemptively transplanted kidneys had a KDPI of 93% ± 4% while the KDPI were 62% ± 14% and 62% ± 9% in patients who received the transplant after being on dialysis for 1-4 years and 4-8 years respectively. Mean dialysis duration was 31 ± 10 mo and 67 ± 13 mo respectively in patient groups with dialysis duration 1-4 years and 4-8 years. As shown there were significant differences between the preemptive transplant group and groups that received kidney transplant after being on maintenance dialysis. In the preemptive transplant group, donor age was higher with fewer male donors along with fewer

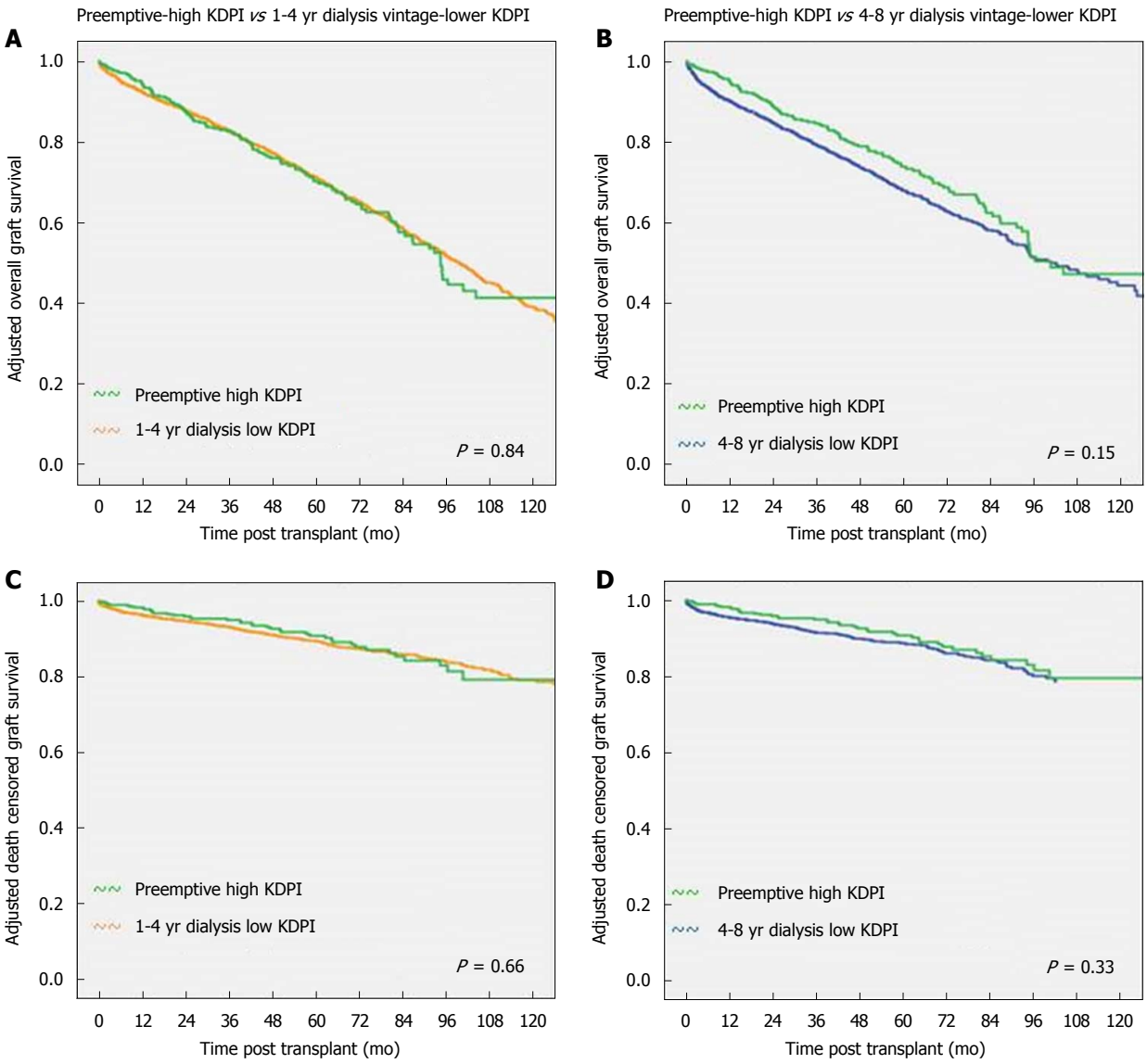

Figure 1 Adjusted graft survival. A: Overall graft survival for recipients of preemptive-high KDPI kidneys compared to 1-4 years dialysis vintage-lower KDPI kidneys; B: Overall graft survival for recipients of preemptive-high KDPI kidneys compared to 4-8 years dialysis vintage-lower KDPI kidneys; C: Death-censored graft survival for recipients of preemptive-high KDPI kidneys compared to 1-4 years dialysis vintage-lower KDPI kidneys; D: Death-censored graft survival for recipients of preemptive-high KDPI kidneys compared to 4-8 years dialysis vintage-lower KDPI kidneys. KDPI: Kidney donor profile index.

donation after cardiac death (DCD) and more expanded criteria donor (ECD) kidneys; recipients were older with fewer males, African Americans, and diabetics. Preemptive group also had higher proportion of kidneys pump perfused, lower PRA, higher HLA mismatches, lower DGF rates and lower steroid maintenance rates.

Graft and patient outcomes

Adjusted overall graft and death-censored graft survivals of preemptive high KDPI kidney recipients compared to recipients of lower KDPI kidneys with 1-4 years and 4-8 years dialysis vintage is shown in Figure 1. Adjusted overall graft failure risk and death-censored graft failure risk in preemptive high KDPI kidney recipients were similar when compared to group that received lower KDPI kidney after being on maintenance dialysis for either 1-4 years (HR 1.01, 95%CI: 0.90-1.14, $P = 0.84$ and HR 0.96, 95%CI: 0.79-1.16, $P = 0.66$ respectively) or 4-8 years (HR 0.82, 95%CI: 0.63-1.07, $P = 0.15$ and HR 0.81, 95%CI: 0.52-1.25, $P = 0.33$ respectively) as shown in Table 2.

Adjusted patient survival of preemptive high KDPI kidney recipients compared to recipients of lower KDPI kidneys with 1-4 years and 4-8 years dialysis vintage are shown in Figure 2. Adjusted patient death risk in preemptive high KDPI kidney recipients were similar when compared to groups that received lower KDPI kidney after being on maintenance dialysis for 1-4 years (HR 0.99, 95%CI: 0.87-1.12, $P = 0.89$) but lower compared to patients who were on dialysis for 4-8 years (HR 0.74, 95%CI: 0.56-0.98, $P = 0.04$) as shown in Table 2.

Table 2 Comparison of graft and patient outcomes between the groups

	Preemptive-high KDPI (n = 349) *vs* 1-4 yr dialysis vintage-lower KDPI (n = 3300)		Preemptive-high KDPI (n = 349) *vs* 4-8 yr dialysis vintage-lower KDPI (n = 2460)	
Adjusted overall graft failure risk	1.01 (0.90-1.14)	0.84	0.82 (0.63-1.07)	0.15
Adjusted death censored graft failure risk	0.96 (0.79-1.16)	0.66	0.81 (0.52-1.25)	0.33
Adjusted patient death risk	0.99 (0.87-1.12)	0.89	0.74 (0.56-0.98)	0.04

KDPI: Kidney donor profile index.

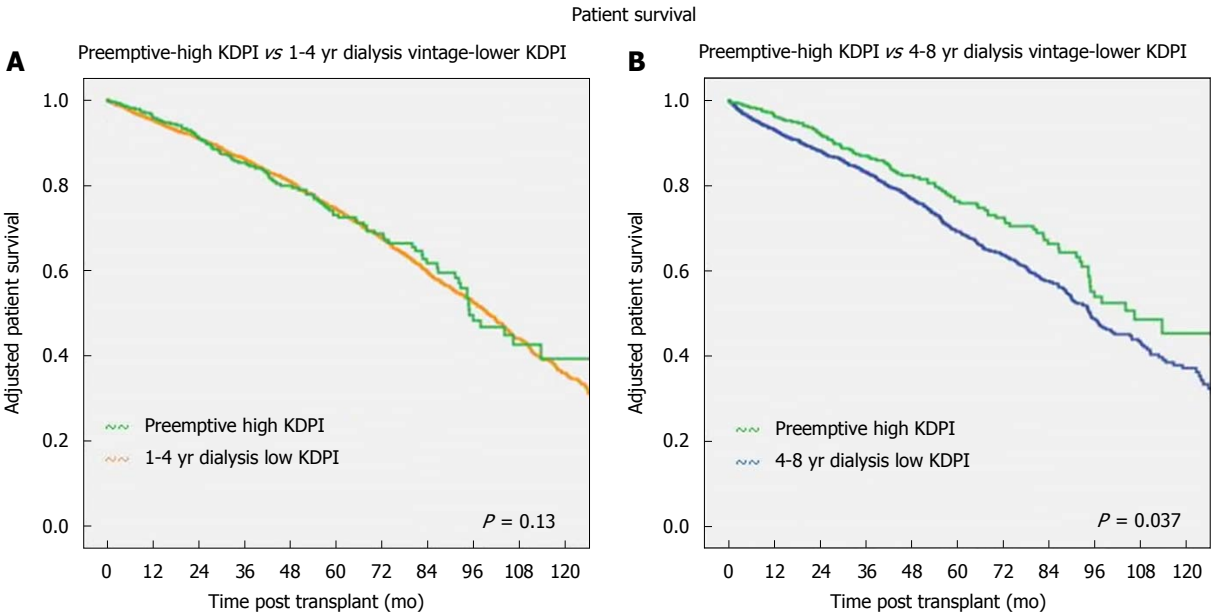

Figure 2 Adjusted patient survival. A: Patient survival for recipients of preemptive-high KDPI kidneys compared to 1-4 years dialysis vintage-lower KDPI kidneys; B: Patient survival for recipients of preemptive-high KDPI kidneys compared to 4-8 years dialysis vintage-lower KDPI kidneys. KDPI: Kidney donor profile index.

DISCUSSION

Our study showed that preemptive transplantation of high KDPI (⩾ 85%) kidneys in older first-time recipients conferred graft and patient outcomes that were not inferior when compared to transplanting better quality lower KDPI (35%-84%) kidneys in older recipients who were on maintenance dialysis for variable periods of time. In fact a patient survival benefit was emerging for preemptive high KDPI kidney recipients when compared to patient who got transplanted better quality kidney after a longer dialysis vintage. Our findings support favorable consideration of "marginal" kidneys for preemptive transplantation in older patients on the waiting list.

Living donor kidney transplantation in general offers the best patient and graft survival with the benefits extending to older recipients as well[11,12]. Living donor kidneys from 60-69 years old donors transplanted into older recipients' conferred superior patient survivals compared to standard criteria donor (SCD) and ECD DDKs while the graft survivals were superior compared to ECD but similar compared to SCD kidneys[13]. Patients without options for living donors are faced with an increasing time on the deceased donor wait list. The median time to transplant once listed has been steadily increasing, for instance from 5.5 years in 2003 to 7.6 years in 2007[11]. This is particularly disadvantageous to older wait listed patients, since longer they wait; the less likely they get transplanted since their health status can deteriorate thus running the risk of removal from the wait list or death[14]. Consideration of high KDPI kidneys can help to decrease the waiting time for such patients.

Transplantation of DDKs with high KDRI (from which KDPI is calculated) is associated with increased risk for allograft failure when compared to transplanting lower KDRI kidneys[2,10]. As mentioned, DDKs with KDPI ⩾ 85% are considered as "marginal" quality organs similar to the kidneys from ECD terminology used prior to the implementation of new KAS. Transplantation of ECD kidneys have been shown to be associated with higher risk for developing DGF, longer hospital length of stay and higher readmissions rates with higher cost of care along with increased risk for graft loss and mortality[15-18]. Because of these concerns, centers could understandably be reluctant to accept marginal kidneys for preemptive transplantation in their wait listed patients who have not started maintenance dialysis yet. However, it is hard to predict how long such patients

will have to wait to get offer for a more desirable kidney with a good chance that they could initiate dialysis while waiting. Our findings support the practice of careful consideration of marginal kidney offers compared to automatic decline of such kidney offers for preemptive transplantation in wait listed older recipients. This may also help to reduce the discard rate for these kidneys with KDPI ⩾ 85% which was at 60% at year 2 after the implementation of new KAS according to a recent UNOS report[19].

Despite a 70% increased risk for graft failure compared to non-ECD kidneys, transplantation of ECD kidneys which are considered "marginal" was found to confer survival benefit when compared to staying on waiting list[12,20-22]. Dialysis duration has been suggested as the strongest independent modifiable risk factor for renal transplant outcomes[8]. Increased comorbidity burden and immunological alterations that can develop in dialysis patients, along with adverse socioeconomic conditions associated with prolonged dialysis are some of the factors implicated towards inferior transplant outcomes observed in patients exposed to longer dialysis duration. Any adverse impact of transplanting high KDPI marginal kidneys in our preemptive group likely got mitigated by dialysis avoidance. On the other hand, any potential benefits of transplanting better quality lower KDPI kidneys in the dialysis groups are likely minimized by the impact of dialysis vintage on transplant outcomes. A previous analysis showed lower overall cumulative mortality associated with transplantation of high KDPI kidneys when compared to equivalent patients who forego high KDPI kidney transplantation with the hope of receiving lower KDPI kidney at a later time point while staying on dialysis[23]. Benefit was more pronounced in recipients > 50 years of age and at centers with wait time > 33 mo.

While our study demonstrated similar graft and patient outcomes for preemptive transplantation of high KDPI kidneys when compared to low KDPI kidney transplantation after varying dialysis vintage in older recipients, one also has to consider the quality of life advantage that can come with earlier transplantation. Previous studies have shown quality of life benefits in older patients who underwent kidney transplantation[24,25]. Earlier kidney transplantation could also translate into long-term cost savings. A recent economic analysis of contemporary kidney transplant practice found cost saving with living donor and low KDPI deceased donor transplants when compared to dialysis while transplantation using high KDPI DDK was cost effective[26].

Our study has limitations that merit discussion. Retrospective design only can prove associations but not causation. However, a prospective study addressing the same question will be difficult to conduct for logistical reasons. Residual confounding can still occur despite using a multivariate adjustment in our analysis. Doses or drug levels of maintenance immunosuppressive drugs and information about longitudinal changes in medication regimens which could impact transplant outcomes were not available. Even though our analysis showed favorable outcomes of preemptive transplantation of high KDPI kidneys in older recipients, this does not imply transplantability of each and every such kidney. The analysis was biased towards kidneys that actually got transplanted and kidneys may be rejected for reasons unrelated to KDPI.

In summary, our study supports accepting a "marginal" quality high KDPI kidney preemptively in older wait-listed patients thus avoiding dialysis exposure. Such preemptive transplantation results in graft and patient outcomes non-inferior to receiving a better quality kidney with lower KDPI after being on dialysis for a variable period. This practice could come with an added quality of life benefit associated with earlier transplantation and possibly cost benefit. In order to best serve such patients on the waiting list, clinicians should be open to offers of high KDPI kidneys and get the patients involved in this important and very personal decision making process.

ARTICLE HIGHLIGHTS

Research background

It is unclear whether preemptive transplantation of high kidney donor profile index (KDPI) (marginal quality) kidneys and thus avoiding maintenance dialysis in older recipients would be beneficial compared to waiting for and transplanting lower KDPI (better quality donor organ) kidneys after being on dialysis for varying lengths of time. We sought to answer this by utilizing the national transplant database.

Research motivation

The aim of this study was to evaluate the outcomes of transplanting marginal kidneys preemptively compared to better-quality kidneys after varying dialysis vintage in older recipients.

Research objectives

The objective of our study was to explore the benefits of transplanting marginal quality kidney preemptively compared to waiting for better quality kidney transplantation after exposure to varying times on dialysis.

Research methods

Using United Network for Organ Sharing database, we identified patients > 60 years who underwent first time deceased donor kidney (DDK) transplantation between January 2001 and December 2015, after receiving induction and discharged on calcineurine inhibitor/Mycophenolate Mofetil immunosuppression. We further identified patients who underwent preemptive DDK with KDPI ⩾ 85% and those who underwent DDK with KDPI of 35%-84% after being on maintenance dialysis for either 1-4 years or 4-8 years. Cox model was used to compare adjusted graft and patient outcomes between the groups. HR with 95%CI was calculated. A *P* value of < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS software version 18.

Research results

Adjusted overall graft failure risk and death-censored graft failure risk in preemptive high KDPI kidney recipients were similar when compared to group that received lower KDPI kidney after being on maintenance dialysis for either 1-4 years or 4-8 years. Adjusted patient death risk in preemptive high KDPI kidney recipients were similar when compared to groups that received lower KDPI kidney after being on maintenance dialysis for 1-4 years but lower

compared to patients who were on dialysis for 4-8 years.

Research conclusions

Our study supports accepting a "marginal" quality high KDPI kidney pre-emptively in older wait-listed patients thus avoiding dialysis exposure. In order to best serve older patients on the waiting list, clinicians should be open to offers of high KDPI kidneys and get the patients involved in this important and very personal decision making process. A pre-emptive kidney transplant-even if it is a marginal organ, could come with an added quality of life benefit associated with earlier transplantation and possibly cost benefit. It is acceptable to use marginal quality kidneys in older transplant recipients, rather than having them wait on dialysis for better quality kidney. It has been widely accepted that marginal quality organs are acceptable for use in older transplant recipients. But there has been hesitance in accepting these kidneys for recipients who are not on dialysis yet. The purpose of this study was to evaluate the impact of avoiding dialysis vintage by preemptive transplantation of marginal kidneys in older recipients when compared to receiving better quality organ while remaining on dialysis. Avoiding dialysis with early transplantation should be favorably considered even with marginal quality kidneys. It will be logistically hard to design a prospective study trying to answer the same question; but that would be ideal. Future study should identify older patients who declined preemptive offer of marginal kidneys and went on to get better quality kidneys at a later point after being on dialysis. Control group should be older patients who accepted those marginal kidneys preemptively. Post-transplant outcomes between the 2 groups should be compared. It is acceptable to use a marginal quality kidney in an older recipient, thereby avoiding dialysis exposure. The current study supports the hypothesis of transplanting marginal quality kidney preemptively in older patients. The findings of this study enable transplant professionals to make a more informed choice when faced with the option of getting a marginal kidney offer for their older wait listed patients with chronic kidney disease who are not on dialysis yet.

Research perspectives

Avoiding dialysis exposure with early transplant even with a marginal kidney is potentially beneficial. Future studies should look at the outcomes of older patients who turned down a marginal kidney for preemptive transplantation and received better quality kidney after exposure to variable dialysis time compared to older patients who accepted the declined marginal kidneys preemptively and thus avoided dialysis exposure. Future study should identify older patients who declined preemptive offer of marginal kidneys and went on to get better quality kidneys at a later point after being on dialysis. Control group should be older patients who accepted those marginal kidneys preemptively. Post-transplant outcomes between the 2 groups should be compared.

ACKNOWLEDGEMENTS

Accepted for presentation as a poster at the American Transplant Congress, June 2018, Seattle, WA. The data reported here have been supplied by the United Network for Organ Sharing as the contractor for the Organ Procurement and Transplant Network. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by OPTN or the United States government.

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P- Reviewer: Kute VB, Shrestha BM **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Tan WW

World Journal of Transplantation

Submit a Manuscript: http://www.f6publishing.com

World J Transplant 2018 August 9; 8(4): 110-121

DOI: 10.5500/wjt.v8.i4.110

ISSN 2220-3230 (online)

ORIGINAL ARTICLE

Observational Study

Renal transplants from older deceased donors: Is pre-implantation biopsy useful? A monocentric observational clinical study

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Author contributions: Colussi G designed the study, wrote the draft, and contributed to data acquisition, data analysis and interpretation; Camozzi MPL, Colombo VG and Casati C contributed to data acquisition, editing, reviewing and final approval of article; Salerno FR contributed to data acquisition and data analysis.

Institutional review board statement: DKT protocol has been issued by the regional regulatory agency NITp with n. PT.(02).06.580; local ethic committee Milano Area 3 has been notified of the study as an anonymous and non-interventional report.

Informed consent statement: Each patient signed informed consent at the time of listing for renal transplantation, and before renal transplantation itself. No further informed consent was required for this study because the analysis used anonymous clinical data that were collected after patients agreed to treatment by written consent.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

STROBE statement: The authors have read the STROBE statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Manuscript source: Invited manuscript

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Received: February 28, 2018
Peer-review started: March 8, 2018
First decision: April 4, 2018
Revised: April 9, 2018
Accepted: May 11, 2018
Article in press: May 13, 2018
Published online: August 9, 2018

Abstract

AIM

To compare survival of kidney transplants from deceased extended criteria donors (ECD) according to: (1) donor graft histological score; and (2) allocation of high score grafts either to single (SKT) or dual (DKT) transplant.

METHODS
Renal biopsy was performed as part of either a newly adopted DKT protocol, or of surveillance protocol in the past. A total 185 ECD graft recipients were categorized according to pre-implantation graft biopsy into 3 groups: SKT with graft score 1 to 4 [$SKT_{(1-4)}$, *n* = 102]; SKT with donor graft score 5 to 8 [$SKT_{(>4)}$, *n* = 30]; DKT with donor graft score 5 to 7 (DKT, *n* = 53). Graft and patient survival were analyzed by Kaplan-Meier curves and compared by log-rank test. Mean number of functioning graft years by transplant reference, and mean number of dialysis-free life years by donor reference in recipients were also calculated at 1, 3 and 6 years from transplantation.

RESULTS
There were no statistically significant differences in graft and patient survival between $SKT_{(1-4)}$ and $SKT_{(>4)}$, and between $SKT_{(>4)}$ and DKT. Recipient renal function (plasma creatinine and creatinine clearance) at 1 years did not differ in $SKT_{(1-4)}$ and $SKT_{(>4)}$ (plasma creatinine 1.71 ± 0.69 and 1.69 ± 0.63 mg/dL; creatinine clearance 49.6 + 18.5 and 52.6 + 18.8 mL/min, respectively); DKT showed statistically lower plasma creatinine (1.46 ± 0.57, $P < 0.04$) but not different creatinine clearance (55.4 + 20.4). Due to older donor age in the DKT group, comparisons were repeated in transplants from donors older than 70 years, and equal graft and patient survival in SKT and DKT were confirmed. Total mean number of functioning graft years by transplant reference at 1, 3 and 6 post-transplant years were equal between the groups, but mean number of dialysis-free life years by donor reference were significantly higher in SKT (mean difference compared to DKT at 6 years: 292 [IQR 260-318] years/100 donors in $SKT_{(1-4)}$ and 292.5 [(IQR 247.8-331.6) in $SKT_{(>4)}$].

CONCLUSION
In transplants from clinically suitable ECD donors, graft survival was similar irrespective of pre-implantation biopsy score and of allocation to SKT or DKT. These results suggest use of caution in the use of histology as the only decision criteria for ECD organ allocation.

Key words: Dual kidney transplant; Extended criteria donor; Graft survival; Pre-implantation biopsy score; Renal transplantation; Single kidney transplant

Core tip: Pre-implantation biopsy of grafts from elderly donors is under appraisal as a means to direct the acceptance/discard decision of organs for transplantation and the best allocation to single rather than dual transplant. Presented data shows that in recipients of grafts from older donors, rated suitable to donate according to clinical data and preserved renal function, graft and patient survival did not differ in the two categories of transplants with graft histological score in the lower (1-4) or higher (5-8) range of a scale in use. Additionally, allocation of higher score grafts to single or dual transplant did not result in different survival in time, but observed total number of dialysis free life years in recipients up to 6 years was lower for the dual kidney transplant (DKT) allocation. We suggest that older donors rated suitable to donation by clinical decision and preserved renal function may be allocated to single kidney transplant without biopsy; if biopsy is performed, higher scores than those in actual use should be considered for allocation to DKT.

Colussi G, Casati C, Colombo VG, Camozzi MLP, Salerno FR. Renal transplants from older deceased donors: Is pre-implantation biopsy useful? A monocentric observational clinical study. *World J Transplant* 2018; 8(4): 110-121 Available from: URL: http://www.wjgnet.com/2220-3230/full/v8/i4/110.htm DOI: http://dx.doi.org/10.5500/wjt.v8.i4.110

INTRODUCTION

Organ shortage is widely held the most urgent problem in the field of kidney transplantation[1]. In order to increase the donor pool and the chance of transplantation to patients on wait list most transplant programs are increasingly accepting suboptimal, so called "extended criteria", donors (ECD)[2,3]. Despite worse performance than transplants from young donors in terms of delayed graft function (DGF), primary non function (PNF), short and long term renal function and overall graft survival[2-4], transplants from ECD may offer a survival advantage in comparison with not-being transplanted and remaining on wait list, at least for specific patient categories[5-7]. In quantitative terms, several reports indicate that graft survival from adequately selected ECD may not be much lower as compared to grafts from "standard" donors[8-10]. In our series, a retrospective analysis of death-censored graft-survival of transplants from clinically suitable, *i.e.*, with preserved renal function and anatomy, donors older than 60 years was only 8.2% lower than that from younger than 60-year donors after 10 years (84.0% *vs* 92.2%). Thus, elderly donors may be a precious source of transplantable organs.

In some countries (among which Italy), dual (DKT) rather than single kidney transplantation (SKT) from ECD has gained popularity as a means of limiting elderly organ discard[11-15]; a simplistic rational is that quantity of functioning nephrons in one kidney from elderly donors may be insufficient to sustain adequate function in recipients, while double such a quantity may provide adequate compensation. Moreover organ senescence and age-related pathology might also benefit from doubling tissue mass. A critical issue is how to measure and quantitate these variables; common assumption is that histology, and its translation into quantitative scores, may allow a more objective evaluation of organ

Table 1 Histologic score in use for kidney allocation to single kidney transplant or dual kidney transplants of "high-risk" donors

Glomerular global sclerosis	0 = no glomeruli globally sclerosed 1 = less than 20% 2 = 20%-50% 3 = > 50%
Arteries/arterioles wall thickness[1]	0 = normal appearance 1 = less than lumen diameter 2 = equal/slightly higher than lumen diameter 3 = higher than lumen diameter/ severe lumen reduction
Tubular atrophy	0 = absent 1 = less than 20% tubuli affected 2 = 20%-50% 3 = > 50%
Interstitial fibrosis	0 = absent 1 = less than 20% parenchymal tissue substituted 2 = 20%-50% tissue 3 = > 50% tissue

[1]The most severe lesion determines the score. The final score is the sum of 4 individual scores: With final score up to 4 (included) organs are allocated to solitary kidney transplantation; from 5 to 7 organs are allocated to dual kidney transplantation; higher than 7 organs are discarded.

quality than clinical data (renal function, anatomy, comorbidities). Several reports have shown similar survival of high histological score organs (assumed to represent poor-quality grafts) used as DKT as compared to SKT with low histological score grafts (again assumed to represent better-quality organs)[11-13]; these results have been credited to support the validity of biopsy-based organ allocation. On the other hand, other reports have shown equal survival of grafts from elder donors (all allocated to SKT) independently of pre-implantation histological score, *i.e.*, low (1 to 3)[8,16,17] *vs* high [4 to 6(8) or 4 to 5[16,17]] score. Score 4 constitutes the limit for differential allocation of ECD grafts to SKT rather than DKT in the biopsy-based protocol in use in our transplant area. We and others[18] have reported that DKT recipients who lost one graft due to surgical complications were able to maintain adequate organ function, despite bad histological score of the surviving graft. Thus, it would appear that current biopsy protocol for allocation of ECD grafts to SKT or DKT may foster unbalanced allocation to DKT of grafts suitable for SKT, somehow reducing transplant benefits from available donors. In the present analysis, we have taken advantage of donor kidney pre-implantation biopsies performed in the past, *i.e.*, before adopting current biopsy-based DKT program, as a component of post-transplant surveillance protocol; we have reviewed all available biopsies from ECD and scored them according to current criteria within the DKT program. Several grafts, allocated to SKT, happened retrospectively to show > 4 histological score, a value which would actually indicate allocation to DKT. The aim of the study was to retrospectively compare the outcome of SKT from ECD categorized according to histological score, *i.e.*, up to 4, or higher than 4; in addition, outcome of SKT from grafts with low or high histological score was also compared to outcome of DKT from grafts with high histological score according to current protocol. Graft survival in time and measured renal function at one year in recipients were main outcomes; in addition, dialysis-free life years in recipients at 1, 3 and 6 years within each transplant category were also evaluated using the restricted mean survival time methodology[19-21].

MATERIALS AND METHODS

Donor categories and transplant types

All renal transplants from older than 60-year donors performed in our Centre from 1 Jan 2000 to 30 Oct 2017 were analyzed, provided that a pre-implantation biopsy was available. Up to 30 Nov 2010 only SKT were performed; irrespective of age and comorbidities, donor suitability was based on clinical data which included normal lower pre-donation plasma creatinine, eGFR (Cockroft-Gault formula) higher than 60 mL/min per 1.73 m^2, proteinuria absent or "trace", and anatomy permissive (echography and/or surgical inspection). Pre-implantation biopsy was not required, and was only performed for cause, *e.g.*, in case of pre-donation acute renal failure or more than trivial proteinuria, to ascertain any specific pathology, or as part of a post-transplant surveillance protocol, in which case histological data were analyzed only time after transplantation.

After 1 Dec 2010 our Centre joined to a biopsy-based DKT program designed and coordinated by our inter-regional regulatory agency, NITp[11], where it is publicly registered[22], and which is shared by all transplant Centers of the area. Within this program older than 60-year donors are allocated to SKT or DKT according to clinical and histological criteria: Donors older than 70 years, or aged 60-70 years with any of arterial hypertension treated with $\geqslant$ 2 drugs, drug-treated type 2diabetes mellitus, death due to cerebrovascular event (with exclusion of trauma and aneurism rupture as cause of brain death), proteinuria higher than 0.5 g/L, eGFR (Cockcroft-Gault) less than 60 mL/min per 1.73 m^2 undergo pre-implantation biopsy, and are allocated to SKT if histological score is $\leqslant$ 4, to DKT if mean score is 5-7, and discarded if mean score is > 7 (Table 1); these donors are collectively defined "high-risk" ECD. When only one of partner kidneys had a score > 4, it was at discretion of the transplant Centre to perform DKT or SKT with the lower score graft. Donors in the 60-70 year-range, without any of the above comorbidities, collectively defined "low-risk" ECD, are allocated to SKT without biopsy.

Application to the program is additive to that for standard donors and requires signature of a specific informed consent; in our Centre we also require recipient's age older than 62 years. Consent includes either DKT or SKT from the same donor categorized as "high-risk" ECD. All donors were brain-dead; transplants from

living, cardiac-death, ABO- or HLA-incompatible donors, as well as simultaneous kidney and any other organ transplants were not included. Both first and non-first transplants were included. A pre-transplant negative T and B-lymphocyte CDC was a pre-requisite for transplantation and forbidden donor antigens, according to actual or historical HLA antibodies in recipient, were carefully avoided by the allocation agency; allocation algorithm in use in our inter-regional area searches for best HLA match first, then for immunization status, listing time and age match in all transplant categories except in DKT protocol, where HLA match is not considered.

Informed consent was obtained from all the patients applying for renal transplantation in our Centre at the time of listing and at the time of transplantation, and additionally for applying to the DKT program. Consent for anonymous use of clinical data was included in the consent form. This study has been conducted according to principles of the declaration of Helsinki and complies with the declaration of Istanbul. As a standard of care, anonymous study no approval by ethic committee was needed.

Study design

We analyzed and compared 3 groups of transplants: Group 1, SKT from older than 60-year donors with pre-implantation graft biopsy score, either before or within the DKT protocol, $\leqslant 4$ ($SKT_{(1-4)}$); group 2, SKT with graft pre-implantation biopsy score, either before or within the DKT protocol, $\geqslant 5$ ($SKT_{(>4)}$); we included within these 2 SKT categories also 6 DKT recipients who had early removal of one graft for surgical complications with score in remaining graft $\geqslant 5$ (5 patients) or < 5 (1 patient); group 3, DKT with graft pre-implantation biopsy score 4 to 7 according to the DKT protocol (DKT). As already said, only in the DKT protocol histological score was known before transplant and used for differential graft allocation, while in the pre-DKT period it was only a retrospective information.

For every donor-recipient pair, in each group, we collected and analyzed clinical data of interest, age, sex, HLA mismatches (loci A, B, DRB1), type and length of dialysis in recipients, plasma creatinine and eGFR in donor and plasma creatinine and creatinine clearance (24 h urine) at 3 mo and 1 years post-transplant in recipients, and biopsy-proven rejection of any type in the first 18 mo after transplantation in recipients. Outcomes of interest were death-censored graft survival (*i.e.*, freedom from dialysis or re-transplantation), overall graft survival (*i.e.*, graft loss or patient death with functioning graft, whichever came first, corresponding to patients alive with functioning graft), patient survival (*i.e.*, death with functioning graft) and renal function in recipients at 3 and 12 mo from transplantation; we also evaluated: Early graft losses (EGL, *i.e.*, no dialysis-freedom, or need of permanent dialysis, within 3 mo after transplantation), DGF (need of dialysis for any cause in the first week after transplantation), mean years of functioning graft at 1, 3 and 6 years from transplantation with reference to initial transplants and total dialysis-free life years at the same times with reference to donors.

Data base update was closed on 31 Jan 2018, allowing for at least 3 mo uncensored follow up in all patients; since only in few cases total follow-up was longer than 6 years in the DKT group, and longer of 10 years in both the SKT groups, follow up was censored at 6 years in DKT and 10 years in $SKT_{(1-4)}$ and $SKT_{(>4)}$.

Biopsies within the DKT program were either wedge or core biopsies, according to harvesting Centre practice, while our historical biopsies were all core needle. Score was evaluated on paraffin-embedded, hematoxylin-eosin stained slides; in the DKT program score was calculated by any of participating Centre pathologists and communicated to NITp; all our pre-DKT surveillance biopsies were viewed and scored by collaborative work of a pathologist (Camozzi MLP) and two nephropathologists (Colombo VG and Casati C). A minimum of at least 10 glomeruli were required for a biopsy to be representative.

Immunosuppression protocols

Immunosuppression protocols at our Centre did not change in all observation period (Jan 2000 to Oct 2017), and included in most patients rATG induction (3.5 mg/kg in 7 d, 7 mg/kg if $\geqslant 2^{nd}$ transplant), cyclosporine-A starting pre-transplantation as a 10 mg/kg oral load, mycophenolate mofetil/mycophenolic acid starting on p.o. day 1 (1g or 720 mg bid) and corticosteroids (methyl-prednisolone 500 mg at reperfusion, rapidly tapered down to 8 mg/d on p.o. day 11 and 4 mg/d after 3 mo). In a minority of patients, tacrolimus, everolimus, belatacept or sirolimus were used (Table 2). Post-transplant heparin anticoagulation was started in 2011 only in DKT, after that a higher than usual graft vein thrombosis was observed in this type of transplant, as described also by others[23].

Statistical analysis

Descriptive statistics are given as numbers, percentages and mean ± SD or median (1^{st} and 3^{rd} interquartile range, IQR) according to data distribution; inter-category differences were checked by ANOVA, followed by Scheffé *post-hoc* test; Fisher's exact test was used for comparison of frequencies; Pearson's coefficient was used for correlation analysis between pairs of data. Survival analysis was estimated as event free cumulative survival using the Kaplan–Meier method and compared using the log-rank Mantel-Cox test.

We estimated the mean number of years the allo-grafts were functioning before loss for any cause (failure or death with functioning graft) by the restricted mean survival analysis[19-21]; it is computed as the total area under the survival curve at specific times (we repeated the procedure at 1, 3 and 6 post-transplant years), and indicates the mean time (years) the grafts remained functional at any defined time. Conceptually, this evaluation indicates mean dialysis-free life years for every

Table 2 Baseline characteristics of donors and recipients in the 3 transplant categories

Transplant category[1]	SKT(1-4)	SKT(> 4)	DKT
n	102	30	53
Donors, M/F	54/48	16/14	29/24
Donor age, yr (mean, SD)	68.9 ± 5.7	66.9 ± 6.7	75.3 ± 5.0[b]
Score of transplanted graft, median (IQR)	3 (3-4)[d]	5 (5-6)[a]	5 (4-5)
Donor comorbidities			
Donor age > 70 yr, *n* (%)	47 (46)	8 (27)	47 (89)[b]
Arterial hypertension	40 (39)	21 (70)	34 (64)
Diabetes	9 (9)	6 (20)	7 (13)
Cerebrovascular cause of death	33 (32)	17 (57)	29 (55)
KDPI[1]	89.4 ± 8.0	89.9 ± 9.2	96.9 ± 3.4[b]
KDRI[1]	1.65 ± 0.27	1.7 ± 0.33	2.02 ± 0.31[b]
Recipients, M/F	68/34	20/10	37/16
Recipient age (mean ± SD, yr)	61.0 ± 7.2	60.2 ± 6.0	67.3 ± 4.6[b]
Years on dialysis, median (IQR)	3.5 (0.1-13.5)	3.4 (0.8-9.5)	2.1 (0.3-8.5)[b]
Dialysis mode, *n* (%)			
Hemodialysis	84 (82)	25 (83)	40 (75)
Peritoneal dialysis	16 (16)	5 (17)	12 (23)
Pre-emptive	2 (2)	0	1 (2)
Renal disease *n* (%)[1]			
GN/systemic	35 (34)	10 (34)	19 (36)
ADPKD	24 (23)	4 (13)	6 (11)
Vascular/hypertension	10 (10)	3 (10)	3 (6)
Diabetes	11 (11)	4 (13)	7 (13)
Other	14 (14)	6 (20)	12 (23)
Unknown	8 (8)	3 (10)	6 (11)
1st-2nd-3rd Tx	95-6-1	28-2-0	51-2-0
HLA-MM (median, IQR)	4 (3-5)	4 (3-5)	4 (4-5)
CITa (mean ± SD, h)	15.0 ± 3.6	15.9 ± 4.2	16.1 ± 3.1

[1]SKT(1-4), solitary kidney transplant, histologic score 1 to 4; SKT(> 4): Solitary kidney transplant, histological score 5 or higher; DKT: Dual kidney transplant, histological score 5 to 7; KDPI and KDRI: Kidney Donor Profile Index and Kidney Donor Risk Index; GN/systemic: Glomerulonephritis or systemic immunological disorder; CIT: Cold ischemia time. [b]$P < 0.01$ *vs* SKT (both categories); [d]$P < 0.001$ *vs* SKT(> 4) and DKT; [a]$P < 0.039$ *vs* DKT.

transplanted patient at any defined time. From this value we extrapolated total dialysis-free life years for every 100 donors at any time in each of the 3 groups of transplants; for this calculation each donor was made equal to 1.6 SKT, according to data of our regional agency on utilization of overall retrieved grafts[24], very close to the 1.67 figure for ECD of another transplant program[8], and to 1 DKT. SPSS Statistics software v.21 was used for all analyses. Two-tailed *P* values < 0.05 were considered significant.

RESULTS

In the DKT protocol (after Dec 2010) there were 196 older than 60-year donors, of which 131 qualified for biopsy showing score 4 or less in 66 (allocated to SKT) and score 5 or higher (up to 7) in 65, of which 59 were allocated to DKT and 6 to SKT, with score 5 in 5 and 6 in 1; we accepted these 6 grafts as SKT to avoid discard, since the corresponding partner grafts, with lower than 5 scores, had already been allocated to SKT or was anatomically unsuitable. Six of the 59 DKT, with early removal of one graft for surgical complications, have been included, according to score in remaining graft, in the SKT(> 4) (5 cases: score 6 in 4 cases and score 5 in 1) or SKT(1-4) (1 case, score 3) categories.

In the pre-DKT period, pre-implantation biopsy was available in 72 older than 60-year donors; in 18 cases available tissue was insufficient for adequate scoring, 35 grafts showed score 4 or less, and 19 score 5 or higher (range 5-8). Thus, our analysis concerns 102 SKT(1-4), 30 SKT(> 4), and 53 DKT. Summary data of baseline donor and recipient characteristics in the 3 transplant categories are given in Table 2 and main post-transplant events of interest in Table 3. Donor and recipient age was higher, and time on dialysis prior to transplant shorter, in the DKT category, while donor and recipient sex distribution was equal. Also KDPI and KDRI were higher in the DKT category, mostly as a consequence of older age (see below). Donors older than 70 years were 102, of which 47 were allocated to DKT and 55 to SKT. Histological score was lower by selection in SKT(1-4) than SKT(> 4) and DKT, and was also higher in SKT(> 4) than in DKT. Median and total follow-up was shorter in DKT, due to contribution to follow-up from the pre-DKT years only in the 2 SKT categories. All other donor and recipient characteristics, including donor comorbidities, recipient dialysis mode, renal disease, HLA mismatches, number of transplants, immunosuppression, graft cold ischemia time, were not different between categories. There were no major differences in events of interest along follow up between categories, apart higher incidence of DGF, *i.e.*, need of dialysis in the first week after transplantation, in SKT(> 4). Early graft losses were 9 (7.1%) in all 126

Table 3 Summary of main post-transplant characteristics and events in the 3 transplant categories

Transplant category[1]	SKT(1-4)	SKT(> 4)	DKT
n	102	30	53
Initial immunosuppression, *n* (%)			
rATG	95 (93)	25 (83)	53 (100)
Basilix imab	8 (8)	3 (10)	0
Cyclosporin	91 (89)	25 (83)	50 (94)
Tacrolimus	9 (9)	2 (7)	3 (6)
Mycophenolate	91 (89)	27 (90)	50 (94)
Everolimus	9 (9)	4 (13)	3 (6)
Sirolimus	1 (1)	1 (3)	0
Belatacept	2 (2)	1 (3)	0
Steroids	84 (82)	28 (93)	50 (94)
Tx duration[2], yr (median, IQR)	4.1 (1.6-7.4)	7.0 (2.6-9.9)	2.7 (1.4-4.8)[a]
Total follow-up, pt-years	467.8	180.5	161.7
DGF[3], %	42.1	56.6[c]	24.5
EGL[3], *n* (%)			
All	8 (7.8)	1 (3.3)	2 (3.8)
PNF[3]	4 (3.9)	1 (3.3)	0
Surgical	4 (3.9)	0	2 (3.8)
BPAR[3], *n* (%)	10 (9.8)	3 (10.0)	3 (5.6)
Graft failure[4], *n* (*n*/100 pt-yr)	10 (2.1)	6 (3.3)	3 (1.8)
Pt-death, *n* (*n*/100 pt-yr)	16 (3.4)	4 (2.0)	6 (3.5)

[1]SKT(1-4), solitary kidney transplant, histologic score 1 to 4; SKT(> 4): Solitary kidney transplant, histological score 5 or higher; DKT: Dual kidney transplant, histological score 5 to 7; [2]Right-censored at 6 (DKT) and 10 (SKT) years; [3]DGF: Need of dialysis in the first post-transplant week; EGL: Graft loss within 3 mo; PNF: Primary non-function from unknown cause; BPAR: Biopsy-proven acute rejection; [4]Censored for death with functioning graft; [a]$P < 0.03$ *vs* SKT (both categories); [c]$P < 0.05$ *vs* DKT.

original SKT, *i.e.*, excluding 6 original DKT included here in the SKT groups, of which 4 (3.2%) where associated to graft vascular thrombosis and 5 (4.0%) where "unexplained" PNF; in DKT there were 2 of 59 surgical (thrombosis and hemorrhage) early losses (3.4%), but overall vascular graft thrombosis occurred in 8 of 118 grafts (6.8%) ($P < 0.10$ *vs* SKT).

Donor histological score did not show any significant correlation with donor age ($r = 0.11$, $P > 0.10$), donor plasma creatinine ($r = 0.05$) and eGFR ($r = -0.01$), recipient creatinine clearance at 3 mo and 1 years after transplantation ($r = -0.05$ and 0.05, respectively; all $P > 0.25$), and donor KDPI and KDRI indices ($r = 0.05$ and 0.10, respectively, $P > 0.10$). Both KDPI and KDRI were strongly correlated with donor age ($r = 0.70$ and 0.78, respectively, $P < 0.0001$), and donor eGFR ($r = -0.31$ and -0.36, $P < 0.001$).

Survival analysis by transplant category

There were no statistically significant differences in graft, patient and overall survival in recipients of SKT(1-4) *vs* SKT(> 4) ($P = 0.41$, 0.78 and 0.31 for graft, overall and patients survival), and between DKT and both SKT(1-4) and SKT(> 4) (respectively $P = 0.40$ and 0.23 for graft, 0.71 and 0.85 for patient and graft, and 0.81 and 0.36 for patient survival) (Figure 1).

To account for differences in donor age, we repeated survival analysis in recipients of older than 70-year donors, *i.e.*, in the highest age risk range according to definitions in the DKT protocol in use: there were 47 older than 70 years donors with organs allocated to DKT and 55 to SKT (47 in SKT(1-4) and 8 in the SKT(> 4) categories); since survival data were equal for SKT(1-4) and SKT(> 4), we pooled together all SKT. Donor age was 76.4 + 4.0 in the DKT group, and 74.2 + 3.6 in the SKT group ($P < 0.004$). Recipient age was 67.3 + 4.8 in DKT and 63.2 + 6.2 in SKT ($P < 0.001$). Histological score was 5 (IQR 4-6) in DKT and 4 (IQR 3-4) in SKT ($P < 0.01$). For homogeneity, follow-up was closed at 6 years in both groups. Again, there were no statistically significant differences in graft ($P = 0.24$), patient ($P = 0.64$) and patient and graft survival ($P = 0.28$) (Figure 2).

Renal function in donors and recipients

Renal function in donors and recipients of each transplant category is shown in Table 4. Donor plasma creatinine and eGFR did not statistically differ between transplant categories.

At 3 and 12 post-transplant months, recipients alive with a non-failed graft showed similar levels of plasma creatinine and measured creatinine clearance in SKT(1-4) and SKT(> 4), while in DKT plasma creatinine was lower than in SKT at both times, with statistical significant difference at 3 mo *vs* both SKT(1-4) and SKT(> 4) and only versus SKT(1-4) at 12 mo. Differences in creatinine clearance did not reach statistical significance (Table 4).

Restricted mean number of functioning graft years by transplant and projection of dialysis-free life years by donors

Table 5 shows that the mean number of functioning graft years by transplant reference at 1, 3 and 6 years from transplantation was equal for all 3 transplant categories; for clarity, calculations were referred to 100 transplants.

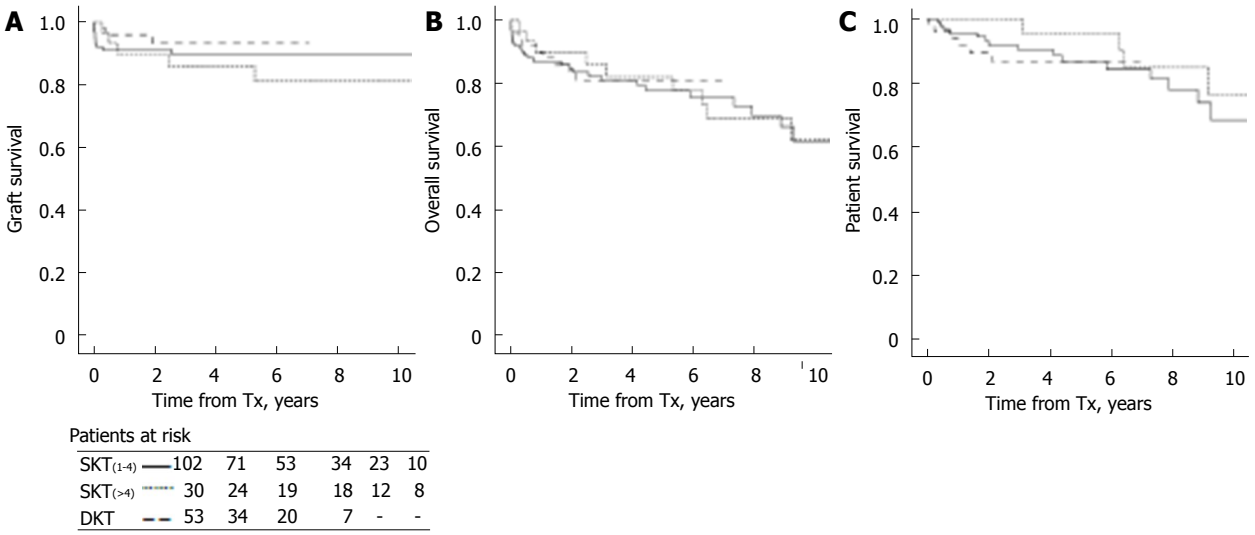

Figure 1 Kaplan Meier plots of graft (death-censored) (A), overall (including death as cause of graft loss) (B) and patient survival (C) according to transplant category. SKT(1-4): SKT with score 1 to 4 grafts; SKT(>4): SKT with score 5 or higher grafts; DKT: Dual kidney transplants with score 4 to 7 grafts. Follow up was censored at 6 years for DKT and 10 years for SKT. There were no statistically significant differences in survival for any of the 3 outcomes. SKT: Single kidney transplant; DKT: Dual kidney transplants.

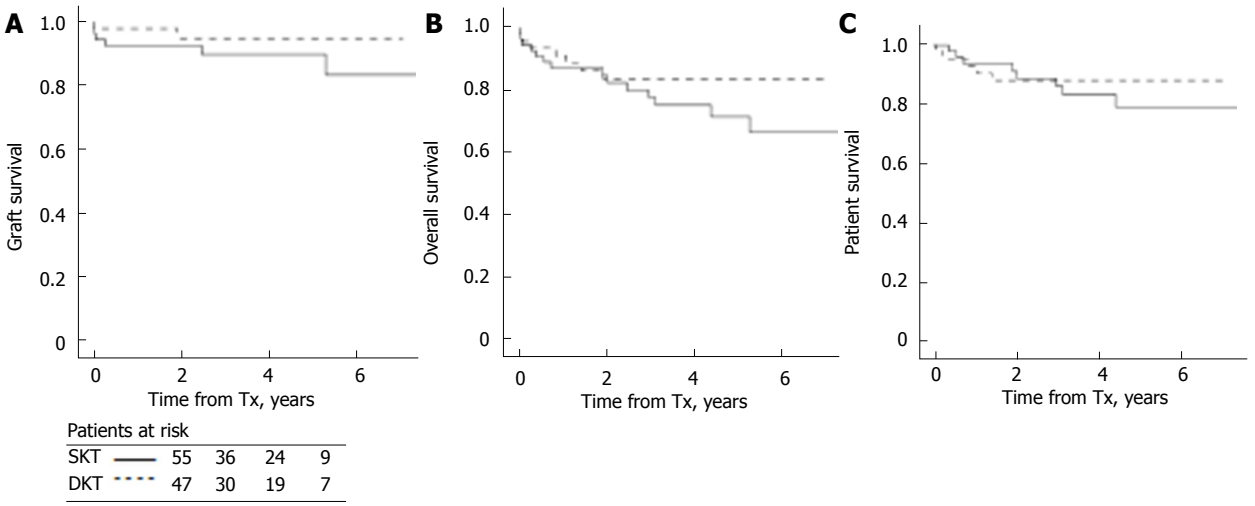

Figure 2 Kaplan Meier plots of graft (death-censored) (A), overall (including death as cause of graft loss) (B) and patient survival (C) in recipients of older than 70-year donors, according to transplant category. SKT: Solitary kidney transplant with any graft score; DKT: Dual kidney transplants with score 4 to 7 grafts. Follow up was censored at 6 years for both SKT and DKT. There were no statistically significant differences in survival for any of the 3 outcomes.

Extrapolation of total dialysis free life years by donor reference at the same time showed significant differences by allocation (*i.e.*, SKT or DKT), with statistically higher figures for both SKT categories at any time. In this extrapolation, we have conservatively chosen an utilization factor of 1.6, rather than 2, SKT for each donor according to published statistics[8,24]. Thus, our data are a minimal realistic estimation of benefits of SKT *vs* DKT, accounting for observed differences in overall survival.

DISCUSSION

Key findings

Our data shows that graft and overall survival in recipients of renal transplants from elderly donors, allocated to SKT, is not statistically different according to histological score of transplanted grafts, *i.e.*, score 4 or lower as compared to score 5 or higher (up to 8); additionally, they also show that survival of grafts of score 5 or higher does not differ by organ allocation to SKT rather than DKT, at least within the available follow-up of 6 years. Also measured GFR at one year from transplantation in not-failed grafts (a generic predictor of survival expectation) does not differ between SKT with differential score grafts, and is marginally better in DKT than in SKT. Thus, our data would indicate that, for organs rated suitable for transplantation clinically, histological information has uncertain usefulness to predict outcome; additionally, current score scale for allocation to DKT appears to hold little discrimination power between grafts which could or could not perform adequately as SKT.

While the biopsy protocol for allocation of elderly donors to SKT or DKT according to score actually in use in our transplant area, which operates on a 19 million

Table 4 Mean ± SD of plasma creatinine and GFR (Cockcroft-Gault formula in donors or 24 h-creatinine clearance in recipients) in donors (D) and recipients (R; at 3 and 12 mo after transplantation) in each transplant category

Transplant category[1]	SKT(1-4)	SKT(> 4)	DKT
D-Pcr, mg/dL	0.88 ± 0.31	0.92 ± 0.28	0.81 ± 0.23
D-eGFR	83.9 ± 27.7	87.1 ± 26.0	79.1 ± 21.8
n	102	30	53
R-Pcr 3 mo	1.92 ± 0.98	2.12 ± 1.12	1.56 ± 0.75[a]
R-CCr 3 mo	45.0 ± 19.3	43.4 ± 21.8	49.6 ± 19.6
n	94	28	49
R-Pcr 12 mo	1.71 ± 0.69	1.69 ± 0.63	1.46 ± 0.57[c]
R-CCr 12 mo	49.6 ± 18.5	52.6 ± 18.8	55.4 ± 20.4
n	83	25	45

[1]SKT(1-4): Solitary kidney transplant, histologic score 1 to 4; SKT(> 4): Solitary kidney transplant, histological score 5 or higher; DKT: Dual kidney transplant, histological score 5 to 7; [a]$P < 0.02$ *vs* SKT(1-4) and SKT(> 4); [c]$P < 0.04$ *vs* SKT(1-4). Pcr: Plasma creatinine; D: Donors; R: Recipients.

population area, dictates allocation of organs with score higher than 4 to DKT, we were able to find out from SKT performed in the past recipients who happened to receive higher than score 4 grafts, as disclosed by surveillance biopsies which were a posteriori scored using criteria of the protocol in use. To these recipients, we added 5 DKT recipients who retained a single high-score graft due to early loss of the corresponding partner graft for vascular complications and 6 other high score grafts in the DKT era whose paired graft had been allocated to SKT in other Centers or was unsuitable for transplantation. The SKT(1-4) recipients were part of both the recent DKT protocol and past transplant activity with available surveillance biopsy. SKT(1-4) and SKT(> 4) groups were well matched concerning donor and recipient characteristics, and differed only in donor graft score by intended, afterward selection; thus, observational data in these 2 groups offer unbiased, clinically relevant, information. DKT category instead showed older age in donors and accordingly in recipients. To overcome this bias, we repeated outcome survival analysis considering only transplants from donors in the most extreme age range, *i.e.*, older than 70 years and up to 88 in DKT and 85 in SKT. In this analysis, due to observed equal graft and patient survival between SKT with different score ranges, we only compared DKT to SKT allocation. Again, there were no statistically significant differences in graft and patient survival between DKT and SKT recipients. Unfortunately, also in this sub-analysis the two populations were not homogeneous, since mean donor and recipient ages were 2 and 4 years older, respectively, and histological score higher in DKT; we think that these small differences have little impact on interpretation of results, even though we recognize that we cannot evade the general assumption that equal outcome with worst graft histology may sustain the validity of DKT allocation by score.

Comparison with literature data

"High risk donors" as defined in our regional DKT protocol (older than 70 years, or 60-69-year-old with comorbidities) are 10 years ahead of canonical ECD definition (older than 60-year or 50-59-year-old with comorbidities)[3,25]. The overwhelming majority of our ECD (84%) were "high risk" according to the above definition. Despite this donor connotation, our medium (in DKT) and long-term data (in SKT(1-4) and SKT(> 4)) shows not inferior graft and patient survival in recipients of these donor grafts than that commonly described for ECD in general[9,10], and confirms the potential wealth of older donor organs. Survival figures did not change, too, by restricting survival analysis to donors older than 70 years, indicating that also very old donors may be safe, if renal function is permissive. Others have described similar survival in recipients of grafts from donors older than 75 years as compared to grafts from younger ECD[10], or in recipients of grafts from ECD donors which differed by decades in the range from 60 to 80 years[12].

Our data that histology appears a poor predictor of transplant outcome confirms other published reports: Hofer *et al*[8] showed similar medium term (8 years) survival of grafts with score 0-3 as compared to score 4-6, with worst survival only for grafts with extremely high score (*i.e.*, 7-12). These latter were only 8 out of 106 ECD (7.5%), and 4 out of 305 SCD (1.3%); it is uncertain if so severe histology entailed any degree of impaired function, which might have indicated for cause biopsy. Carta *et al*[17] report equal short term (3 years) graft and patient survival in SKT recipients of score 4-5 as compared to score 0-3 grafts. Foss *et al*[26] allocated to SKT by clinical criteria 54 grafts from older than 75-year donors and retrospectively could not find any relationship between 5 years graft survival and pre-implantation score (ranging 0 to 8), with equal 1-year plasma creatinine levels in recipients of score 0-4 as compared to score 5-8 grafts.

No single component of histological score has been shown to be consistently associated to post-transplant outcome[8,17,27]; definition of a score limit for graft allocation or for acceptance/discard has so far entailed some empiricism. The original DKT protocol in NITp area contemplated a score above 3 for organ allocation to DKT[28,29], and has been changed to score 4 as a result of favorable outcome of SKT with score 4 grafts[14,30]. Our and others'[8,17,26] data suggests that even higher score grafts, from clinically suitable donors, may perform well as SKT. So, further appraisal from clinical series comparing outcome of grafts with equal histology but differentially allocated to SKT or DKT appears at least desirable. Ideally, such a comparison of outcome should be implemented with the new concept of population-average dialysis-free life years by donors, which may somehow temper the interpretation of the more direct and usual concept of time survival by recipients (see below).

Clinical correlates of histological score

As reported[8,16,17,26] also in our hands histological score,

Table 5 Restricted number (95%CI) of functioning graft years at 1, 3 and 6 years post-transplantation, and projected number of total dialysis-free life years in recipients for every 100 transplants or 100 donors in each transplant category. Differences indicated in bold indicate a statistically significant difference ($P < 0.05$)

		1 yr	3 yr	6 yr
RNFGY (× 100 Tx)	$SKT_{(1-4)}$	93.3 (86.9-99.7)	261.0 (253.3-268.7)	499.6 (490.5-508.7)
	$SKT_{(> 4)}$	93.8 (85.2-102.4)	279.5 (266.9-292.1)	499.9 (482.5-517.2)
	DKT	97.7 (91.4-104.1)	275.0 (264.1-285.8)	507.3 (496.0-524.3)
TDFLY (× 100 donors)	$SKT_{(1-4)}$	149.3 (139.1-159.6)	417.6 (405.4-429.9)	799.3 (784.7-813.9)
	$SKT_{(> 4)}$	150.1 (136.2-163.9)	447.2 (427.1-467.4)	799.8 (772.1-827.6)
	DKT	97.7 (91.4-104.1)	275.0 (264.1-285.8)	507.3 (496.0-524.3)
Vs DKT, difference				
	$SKT_{(1-4)}$	**51.6 (35.0-68.2)**	**142.7 (119.5-165.8)**	**292.0 (260.4-317.9)**
	$SKT_{(> 4)}$	**52.3 (32.2-72.5)**	**172.3 (141.2-203.3)**	**292.5 (247.8-331.6)**

RNFGY: Restricted number (95%CI) of functioning graft years; TDFLY: Total dialysis-free life years; DKT: Dual kidney transplant.

despite being credited as a senescence index, had no relationship with donor age, nor did it correlate with renal function in donors and recipients. It was shown to correlate mostly with hypertension and vascular disease in donors[8,16], a finding consistent with the marginally lower incidence (just below statistical significance) of hypertension in our $SKT_{(1-4)}$ donors in comparison with $SKT_{(> 4)}$ and DKT. It was even not correlated with donor KDPI and KDRI, as shown by equal values of these indices in either SKT category. Higher KDPI/KDRI in DKT were almost the exclusive effect of older donor age, as indicated by the very strong correlation of these indices with donor age, much stronger than that with donor eGFR. Thus, our data adds evidence that current tools to predict organ quality, *i.e.*, histology, KDPI and even pump perfusion[31] have little reliability in predicting individual graft outcome and are no better than clinical evaluation.

Lack of correlation between histological score and graft outcome we have shown has to be commented within the frame of donors with well-preserved renal function; while there is no doubt that donor grafts with severe pathology are poor candidates for transplantation, it is disputable that such grafts associate with well-preserved renal function. In healthy kidney live donors it was shown that while number of glomeruli falls with age, single nephron GFR does not change up to 70 years, so that total GFR proportionally falls[32]; thus preserved GFR may select donors with a lesser degree of age-related nephron loss. Our results indicate that reliance only in histology for organ allocation may not always be well founded, and that even though function does not predict histology it remains a reliable predictor of graft outcome. In ECD with well-preserved renal function, as the majority of ECD in the present series, biopsy should better be avoided. Causes of discordance between histology and outcome have already been commented, and may reside in any of recognized biases of histology, including its randomness, differences in technique and process, and pathologist expertise among others[8,26,27].

We underscore that donors (of any category) who present with impaired renal function, either long standing, acute or uncertain, are a different context. Biopsy in these donors is of definite help in defining specific underlying pathologies (*i.e.*, acute *vs* chronic, reversible *vs* irreversible lesions); while grafts with acute, reversible pathologies (more commonly acute tubular necrosis) perform well as SKT[33], grafts with chronic lesions require integration of both clinical and histological information to guide mainly in the decision between DKT *vs* discard. We think that donors with pre-existing marginal renal function and anatomy should be the main candidates to histological evaluation, with the aim to ascertain that at least 50% of renal mass is viable. We acknowledge that such an achievement may not be easy; within the frame of current score scale, we suggest that a level of at least up to 2 for any individual score should be allowed, summing up to a total of 8 as acceptable score for DKT.

Benefits of SKT vs DKT allocation

DKT was proposed as a means to reduce discard rate of grafts from marginal donors (defined on the basis of vascular disease and/or older age)[34]; organs from these donors have been often perceived to offer inadequate function if used as SKT. Indeed, survival in time of these organs allocated to SKT is lower in comparison with grafts from younger, or standard, donors[9,10]. In one study early graft loss from any cause was 10.1% (4.2% from unexplained PNF) in recipients of ECD grafts against 4.1 (all causes) and 1.5 (PNF), respectively, in standard donor grafts[35]; these and other's[36] figures in ECD transplants are not far from ours in all SKT (7.1% early loss for any cause, with 4.0% PNF). As for survival in time, the population-average relative risk of graft failure (including patient death) at 10 years from transplantation was 1.7 times higher in recipients of an ECD graft as compared to a standard donor graft[8,10]. Translated into quantitative numbers, after 10-year follow-up the mean time to graft failure was only 8 mo shorter for recipients of an ECD graft as compared to standard donor graft[10]. Thus, despite inherent detriments as compared to younger donor grafts, absolute benefits of ECD organs at a population level are not trivial, and foster in many European transplant communities a call to a wider use rather than to discard of these organs[10,20]. In this perspective DKT, even assuming that it effectively reduces early and long-time losses, may not allow an equally efficient use of available organs as

SKT. It is claimed that, due to bad histology, these organs could not perform adequately if allocated to SKT. We have shown instead that SKT of grafts with bad histological score is associated with similar graft and patient survival in recipients as compared to DKT.

We have tried to quantitate benefits from ECD transplants according to allocation to SKT or DKT; from the observed survival curves, we calculated mean number of functioning graft years at specific time points in recipients by transplant reference and mean dialysis-free life years by donor reference. Dialysis-free life years may be viewed as a good indicator of transplant benefits, as far as it includes both quality of life related to transplantation and social cost savings. Dialysis-free life years were greater in SKT than DKT at any time of our analysis, and the difference increased rather than lessen in time. This data would favor SKT over DKT from the same donors; moreover, since our follow up was not long, longer-reaching series are needed to confirm maintenance in time of these benefits. Better renal function at 1 years justifies a longer survival expectation in time for DKT; on the other hand, it has to be appreciated that in the long-term immunological mechanisms are a prevalent cause of graft loss[37], and may become the main determinant of graft survival. Thus, any long-term scenario remains simple speculation unless longer term observational data is available.

Study strengths and limitations

Despite a rather small number of cases, this study allows an unbiased comparison of clinical outcome of renal transplants categorized by graft histology and allocation. Donor and recipient characteristics, immunosuppression and clinical management were homogeneous between groups, except for donors' and recipients' older age in the DKT group. In addition to canonical survival analysis by Kaplan Meier methodology, this study has evaluated novel outcome data in use in clinical transplantation based on the restricted mean survival time methodology, allowing to infer on quantitative dialysis-free life years made possible by differential allocation.

Main limit of the study is the rather short follow up of our DKT population, which advocates for a longer time analysis. Older age in donor and recipients of DKT may also constitute a bias in comparison to SKT categories, however reanalysis of results in older than 70-year donors, with very small mean donor and recipients age difference, confirmed the results in the whole series.

In conclusion, our data shows that grafts older than 60 years of age from deceased donors, allocated to SKT on the basis of clinical suitability, perform equally well in recipients irrespective of categorization according to histological score, up to 4 or greater than 4, and that high-score grafts perform equally well in recipients irrespective of allocation to SKT or DKT. With respect to observed survival figures at 1, 3 and 6 years, overall dialysis-free life years per any donor number were greater for SKT than DKT allocation of equally scored grafts. For clinically suitable organs, histology appears unable to predict and improve the population-average graft survival. Thus, indications for DKT allocation of ECD grafts should perhaps be revised, with DKT being limited to use mainly for organs clinically unsuitable for SKT due to inadequate function and/or imaging/anatomy. In this context, new criteria have to be sought to guide decision not on allocation, but rather on acceptance *vs* discard.

ARTICLE HIGHLIGHTS

Research background

In renal transplantation a hot topic is the best use of older donor grafts: these organs are associated with an higher risk of early and late graft failure, yet this donor category has become the most prevalent one in western countries. Pre-implantation biopsy of grafts from elderly donors is commonly used to guide in the acceptance/discard of organs, and/or in their allocation to single or dual kidney transplant.

Research motivation

There is no universal agreement in the literature on usefulness of biopsy to predict post-transplant graft outcome; additionally, a main concern with dual kidney allocation is a reduction of transplants made possible by available donors.

Research objectives

The main objectives of our study were to retrospectively compare outcome data of transplants with older donor grafts categorized according to pre-implantation histology into a low-score or high-score category; additionally, high-score grafts were compared by allocation to either dual kidney or single kidney transplant category.

Research methods

All renal-only transplants in our Center from 1 Jan 2000 to 30 Oct 2017 from donors older than 60 years and with available pre-implantation graft biopsy were retrospectively evaluated. Before Dec 2010 grafts were allocated only to single kidney transplant, irrespective of histology; after that date we adopted a biopsy-based protocol (DKT protocol), which dictated allocation to single kidney transplant of grafts with low histological score (1 to 4), and to dual kidney transplant of grafts with high histological score (4 to 7).

Research results

A total of 185 patients with pre-implantation biopsy were available, 102 with low histological score (4 or less), 83 with high histological score (5 to 8), of which 30 were allocated to single kidney transplant (score 5 to 8) and 53 to dual kidney transplant (score 5 to 7). Donors allocated to single kidney transplant did not differ between the low score and high score categories as concerns age, sex distribution, renal function, comorbidities, KDPI and KDRI indices, while they were older and with higher KDPI/KDRI indices in the dual kidney transplant category. Up to 10 years after transplant, we did not observe any differences in graft, patient and overall survival between recipients of a single kidney transplant with either low or high histological score, or between recipients of high histological score grafts allocated either to single or dual kidney transplant. These results were confirmed in a sub-analysis based only on the oldest donors (older than 70 years). We also calculated the total number of dialysis free life years in recipients of either a single or dual kidney transplant by available donors, showing a significantly higher value for recipients of a single kidney transplant up to the available follow-up of 6 years.

Research conclusions

Our study shows that the histological score in use in our transplant area does not predict post-transplant outcome in recipients of a single kidney transplant; additionally, allocation of grafts with similar histological score to single or dual kidney transplant is associated with equal survival up to the available follow-up of 6 years. We propose that renal biopsy is not indicated in older donors with preserved renal function and anatomy, and that organ allocation to single kidney transplant allows the best use of these donors. We propose that pre-implantation biopsy be limited to donors of any age with abnormal renal function, to ascertain

type and reversibility of underlying pathology; dual kidney transplant allocation should be considered for bad function grafts with chronic histological pathology, provided that at least 50% viable tissue be reasonably ascertained.

Research perspectives

Main lesson of our study is that histological score scale in current clinical use does not allow to discriminate between organs which could or could not function adequately as single kidney transplant. This implies the risk of underutilization of available donors. A prospective randomization of equal score grafts to single or dual kidney transplant, and a longer follow-up are strongly desirable to ascertain any advantages or inconveniences of dual *vs* single kidney allocation.

ACKNOWLEDGEMENTS

The Authors wish to thank Michele Nichelatti, PhD, specialist in Health Statistics, for helpful suggestions and expert supervision of all statistics of this article, and Maruska Nizzi for expert language editing of the article.

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P- Reviewer: Kute VB, Stavroulopoulos A, Veroux M **S- Editor**: Ji FF
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