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REVIEW

Therapeutic apheresis in kidney transplantation: An updated review

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Abstract

Therapeutic apheresis is a cornerstone of therapy for several conditions in transplantation medicine and is available in different technical variants. In the setting of kidney transplantation, immunological barriers such as ABO blood group incompatibility and preformed donor-specific antibodies can complicate the outcome of deceased- or living- donor transplantation. Postoperatively, additional problems such as antibody-mediated rejection and a recurrence of primary focal segmental glomerulosclerosis can limit therapeutic success and decrease graft survival. Therapeutic apheresis techniques find application in these issues by separating and selectively removing exchanging or modifying pathogenic material from the patient by an extracorporeal aphaeresis system. The purpose of this review is to describe the available techniques of therapeutic aphaeresis with their specific advantages and disadvantages and examine the evidence supporting the application of therapeutic aphaeresis as an adjunctive therapeutic option to immunosuppressive agents in protocols before and after kidney transplantation.

Key words: Kidney transplantation; Therapeutic plasma exchange; Double-filtration plasmapheresis; Immunoadsorption; Extracorporeal photopheresis; Desensitization; Antibody-mediated rejection; Focal segmental glomerulosclerosis

Core tip: Kidney transplantation is the treatment of choice for patients with end-stage renal disease. However, pre-transplant immunological barriers and post-transplant clinical conditions still influence negatively graft and patient's survival. Therapeutic aphaeresis can be applied in many of these conditions using a variety of devices and procedural approaches. This topic review will present a critical evaluation of the available modalities and examine the evidence supporting the application of therapeutic

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aphaeresis in kidney transplantation as an adjunctive therapeutic option in protocols both for pre-operative procedures and during the post-transplant period.

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INTRODUCTION

Therapeutic apheresis (TA), from the Greek αφαιρώ, *i.e.*, remove, is a therapeutic method by which pathogenic blood components such as cells, harmful antibodies and inflammatory mediators causing morbidity, are separated and selectively removed, exchanged or modified by an extracorporeal apheresis system. The clinical applications of TA include renal diseases in native kidneys, metabolic diseases, autoimmune and rheumatic diseases, hematological diseases, neurological disorders, overdose and poisoning, and cover the field of solid organ transplantation[1].

TA techniques widely used in transplantation medicine, as an adjunctive therapeutic option include therapeutic plasma exchange (TPE) and selective TA techniques such as double-filtration plasmapheresis (DFPP), immunoadsorption (IA), and extracorporeal photopheresis (ECP)[1] (Table 1). In the specific field of kidney transplantation (KT), TA is principally employed as an adjunctive therapeutic option to immunosuppressive agents in protocols both for preoperative procedures and during the posttransplant period in the clinical conditions reported in Table 2.

The objectives of this review are the description of technical characteristics, mechanisms of action, advantages, disadvantages, and complications of the TA techniques used in KT, and the rationale examination and evidence supporting the application of TA in treating clinical conditions in KT through the presentation of the current therapeutic protocols.

THERAPEUTIC PLASMA EXCHANGE

Mechanisms of action

TPE, through the removal and replacement of plasma, removes high-molecular-mass pathological substances (> 15000 Da) such as pathogenic antibodies, immune complexes, paraproteins, cytokines and adhesion molecules, and exogenous poisons[2]. In some clinical conditions such as in thrombotic thrombocytopenic purpura (TTP), replacement with normal plasma is indicated to supply the deficient or missing plasma components[2].

However, evidence suggests that TPE also has immunomodulatory effects also. TPE has been associated with a variety of autoimmune diseases with a decline in B cells and natural killer (NK) cells, an increase in T cells, an increase in T suppressor cell function, and an increase in regulatory T cells (Tregs)[3-6]. The immunomodulatory effects of TPE determine an increased susceptibility of cell-mediated and humoral immunity to immunosuppressive agents, and numerous therapeutic protocols integrate the administration of these agents with TPE to enhance their immunosuppressive effects.

The influence of TPE on the Th1/Th2 cytokine-producing-cell balance is controversial. Some studies suggest that TPE induces a shift of the Th1/Th2 balance in favor of Th2 differentiation and the suppression of the Th1 cytokines (IFN-γ and IL-2)[7,8] which evoke cell-mediated immunity and phagocyte-dependent inflammation[9]. Conversely, other studies indicate that TPE is associated with a shift in cytokine-producing peripheral blood lymphocytes from a Th2 dominant pattern (IL-4, IL-6, IL-10), primarily involved in the humoral immune response, to a Th1 predominance[10,11]. Accordingly, further studies are required to elucidate whether TPE contributes to the shift of Th1/Th2 balance and in what way.

Techniques of plasma removal: Centrifugation- vs filtration-based devices

TPE can be achieved by employing centrifugation- or filtration-based devices. Centrifugal TPE (cTPE) is an automated system designed to separate plasma from whole blood utilizing centrifugal force as the basis of operation[2,12]. During treatment,

Table 1 Therapeutic apheresis techniques performed in the setting of kidney transplantation

TPE
cTPE
mTPE
Selective therapeutic apheresis techniques
DFPP
IA
IA using immobilized antibodies
IA using immobilized staphylococcal protein A
IA using immobilized antigens and synthetic epitopes
ECP

TPE: Therapeutic plasma exchange; cTPE: Centrifugal therapeutic plasma exchange; mTPE: Membrane therapeutic plasma exchange; DFPP: Double filtration plasmapheresis; IA: Immunoadsorption; ECP: Extracorporeal photopheresis.

blood is withdrawn from the patient and pumped through an extracorporeal circuit into a rapidly rotating centrifuge chamber, enabling a nonselective plasma separation and removal based on the density of the individual blood substances. The rest of the blood elements returns to the patient by intermittent or continuous flow mixed with a replacement fluid (RF), typically albumin or fresh frozen plasma (FFP), which is required to avoid hypotension[2,12].

Conventional membrane TPE (mTPE) uses highly permeable membranes, with pore sizes of 0.2-0.6 μm diameter, sufficient to separate plasma notselectively from the cellular blood components based on molecular size[13]. The choice of RF depends essentially on the indication for TPE and patient clinical parameters, and does not differ between cTPE and mTPE[13]. A head-to-head comparison of cTPE and mTPE provides a comparable treatment quality[14]. However, mTPE devices are less effective at removing higher-molecular-mass proteins such as IgM and immune complexes[15].

Plasma removal efficiency (PRE; the percentage of plasma removed *vs* plasma processed) is much higher with cTPE than with mTPE. For each 1-1.5 plasma volume exchanged or 2.5-4.0 L, during a session, almost 60%-70% of the original plasma components will be removed with a cTPE device[16]. When the procedure is extended beyond 1.5 plasma volumes, the amount of the removed plasma components decreases as large-molecular-mass substances are slowly equilibrated between their extra vascular and intravascular distribution[16]. In mTPE, to avoid filter clotting and to prevent hemolysis due to high transmembrane pressure (TMP), the PRE is limited to 30%-35%[13]. A consequence of this disparity in PRE is that mTPE devices need to process three or four times the patient's blood volume to obtain an equivalent reduction in the target molecule[17]. As a result, procedure times lead to be longer and/or require higher blood flow rates (BFRs) on mTPE devices.

Choice of vascular access: To achieve higher BFRs, mTPE devices are almost all in need of a central venous catheter (CVC) that is able to maintain BFRs typically in the 150-200 mL/min range, while the lower BFR needed for a cTPE device (50 mL/min) can often be achieved through 17 gauge peripheral vein needles[17,18]. Recently, an update of the World Apheresis Association (WAA) registry data showed more severe adverse events (AEs) in the procedures performed with a CVC[19]. Common severe AEs of CVCs include central-line-associated bloodstream infections (CLABSIs), deep vein thrombosis (DVT), and arterial or venous bleeding[13,19]. Nevertheless, mTPE with a CVC vascular access is the preferred technique in patients with renal failure who require hemodialysis and TPE as they can receive both treatments sequentially using the same dialysis machine.

Choice of anticoagulation: cTPE commonly uses regional citrate anticoagulation (RCA), which binds ionized calcium, a necessary cofactor in the coagulation cascade, to prevent clotting. Bleeding disorders are not common with RCA. However, citrate utilization is often complicated with systemic hypocalcemia (60%-70% of the overall complications during cTPE) resulting from intravascular citrate accumulation potentially leading to severe complications ranging from perioral and/or acral paresthesias to frank tetany and a QT prolongation of the electrocardiogram (ECG) with life-threatening arrhythmia requiring intravenous calcium replacement, often continuous infusion, with the return fluid[19-21]. Hypocalcemia can be further exacerbated if the replacement fluid is FFP, which contains up to 14% citrate by

Table 2 Clinical indications for therapeutic apheresis in kidney transplantation

Desensitization in ABO-i kidney transplantation
Desensitization in patients with preformed HLA-antibodies
Desensitization of deceased donor kidney transplant recipients
Desensitization of living donor kidney transplant recipients
AMR
Recurrence of primary FSGS
Prevention of recurrence and recurrence of complement-mediated aHUS
De novo TMA
Antiphospholipid syndrome and systemic lupus erythematosus
Recurrent and *de novo* anti-GBM disease
Recurrence of ANCA- AAVs

ABOi: ABO incompatible; HLA: Human leukocyte antigens; AMR: Antibody-mediated rejection; FSGS: Focal segmental glomerulosclerosis; aHUS: Atypical haemolytic uremic syndrome; TMA: Thrombotic microangiopathy; GBM: Glomerular basement membrane; ANCA: Antineutrophil cytoplasmic antibody; AAVs: ANCA associated vasculitis.

volume[12,13].

In mTPE, systemic anticoagulation with unfractionated heparin (UFH) is routinely used to maintain circuit patency, while citrate is not preferred because the higher BFRs, as well as the lower PRE, lead to a greater fraction of citrate being returned to the patient[13]. During TPE, antithrombin III (AT III) levels decrease significantly, and heparin itself is filtered with a sieving coefficient (SC) of 1. As a consequence, in comparison to hemodialysis, in mTPE, higher doses of heparin may be required to achieve a clot-free circuit that in association with the bulk removal of plasma, which also involves the nonselective removal of clotting factors, results in a higher risk for bleeding[13]. The risk of heparin-induced thrombocytopenia (HIT) type II is less frequent with low molecular weight heparin (LMWH) in comparison to UFH[18].

Additional differences between cTPE and mTPE are the increased risk of platelet (PLT) loss in centrifugal devices and the potential activation of complement and leukocytes on the artificial membrane described for mTPE[22,23].

SELECTIVE TA TECHNIQUES

Over time, selective TA techniques have been developed to avoid the removal of key plasma constituents that occur with conventional TPE by targeting a specific molecule, antibody, or cellular element[24]. Below, we focus on selective TA techniques that find application in transplantation medicine.

Double filtration plasmapheresis

Double-filtration plasmapheresis (DFPP), or cascade filtration plasmapheresis, is a variation of mTPE, introduced in Japan by Agishi *et al*[25] in the 1980s, for desensitization in ABO-i KT, and over time it has been used for other indications. The circuit contains two plasma filters with different pore sizes, a primary membrane plasma separator to isolate the plasma, and then the plasma fractionator (PF), which is a high molecular-mass filter that removes target macromolecules based on molecular size and mass, primarily immunoglobulins (Ig)[23-25]. The advantage of DFPP is that the PF allows smaller molecules, such as albumin, to pass through the membrane and return to the patient. This results to minimize, or potentially eliminate, the need for an RF and the associated complications, including allergic reaction and infection[23-25]. A disadvantage of DFPP is that the performance of the PF is not sufficient to remove small-molecular-mass IgG and substances smaller than albumin[23-25].

Immunoadsorption

Immunoadsorption (IA) is a TA technique that enables the selective removal of humoral factors from separated plasma through a secondary device with high-affinity absorbers. The adsorption columns contain a specific ligand for the substance to be removed, and the depleted plasma is then returned to the patient[24]. An advantage of IA is that RF is not required because the plasma volume remains the same and albumin is not adsorbed. Over time, different IA devices have been developed.

IA using immobilized antibodies: IA columns containing immobilized antibodies

selectively bind a circulating molecule and remove it from the plasma[24]. A TheraSorb™-Ig adsorber column, containing polyclonal sheep anti-human IgG antibodies immobilized on sepharose, has been shown to be effective in depleting all subclasses of IgG and has been used in ABO-i KT[26]. IA using bound antibodies can also be applied for the depletion of preformed or newly synthesized cytotoxic antibodies in the rejection of allogeneic organ transplants[24]. These columns are utilized in pairs, one working while the other is being regenerated with washing fluids, shifting periodically during the procedure. The online regeneration of the columns enables large volumes of plasma to be treated so that IgG extraction more efficient[24]. Usually, up to two plasma volumes are processed during an Ig apheresis treatment.

IA using immobilized staphylococcal protein A: IA columns containing immobilized staphylococcal protein A (SPA), which has a high avidity for the Fc portions of IgG1, IgG2, and IgG4, have been used to deplete IgG auto antibodies or circulating immune complexes that contain IgG[24]. Furthermore, SPA has been shown to be a B-cell super antigen[27]. The interaction of SPA with peripheral B cells, expressing B cell receptors (BCRs) with VH regions capable of binding SPA, induces B cell apoptosis through the dissipation of mitochondrial membrane potential, the induction of the caspase pathway, and DNA fragmentation[27]. Thus, the exposure of the patient's blood to SPA during IA may also trigger a beneficial immunosuppressive effect. The Immunosorba column, containing SPA bound to sepharose, has been used in acute AMR in KT and in highly sensitized patients waiting for KT[28-31]. During a treatment, two absorbers work alternately. While one is adsorbing, the other is regenerated through the elution of bound antibodies, and vice versa.

IA using immobilized antigens and synthetic epitopes: IA columns containing immobilized antigens and synthetic epitopes are the most specific way to remove Ig as these columns are developed to extract only the antibodies that are reactive with that specific antigen, leaving untouched all other plasma components[24].

The Globaffin column is a regenerative twin adsorber system that utilizes the synthetic peptide GAM which covalently binds to an insoluble sepharose carrier matrix. Peptide GAM has a strong binding affinity, especially to the constant (Fc) section of subclass 1, 2 and 4 IgG antibodies, and finds clinical application in different conditions, including acute AMR and perioperative Ig depletion, in sensitized renal transplant recipients[32].

The glycosorb ABO column contains synthetic terminal trisaccharide A/B blood group antigens covalently linked to a sepharose matrix and has been developed to remove A or anti-B antibodies in recipients of organ transplants from ABO-i donors[33]. However, in a minority of patients, antibody elimination has been demonstrated to be incomplete with the glycosorb ABO column[34]. The inadequate adsorption of core-chain-dependent A/B antibodies may explain this finding[35], but further studies are needed.

ECP

ECP is a cell therapy procedure that begins with the separation of peripheral white blood cells (WBCs) and nonnucleated cells from plasma by centrifugation. Then, the isolated suspension of WBCs undergoes extracorporeal treatment with 8-methoxypsoralen (8-MOP) followed by exposure to ultraviolet A (UVA) light prior to reinfusion in the patient[36]. The combination of 8-MOP and UVA results in the cross-linking of pyrimidine bases in DNA, leading to the apoptosis of lymphoid cells, largely T-cells and natural killer (NK) cells[37]. Upon reinfusion, the phagocytosis of apoptotic lymphoid cells is performed by immature dendritic antigen-presenting cells (iDCs), which subsequently undergo maturation and present self-antigens in a pro-tolerant signaling environment[38]. The activated T cells differentiate into several cell lineages, particularly Tregs, which mediate a specific immunological tolerance by inducing anergy or apoptosis in self-reactive lymphocytes[38].

ECP was initially used in patients with cutaneous T-cell lymphoma (CTCL)[39]. However, over the years, the indications for ECP have increased as it promotes anti-inflammatory and tolerogenic responses without causing global immunosuppression[40]. In solid organ transplantation, ECP has been successfully used to treat acute heart allograft rejection and chronic allograft dysfunction after lung transplantation[41,42]. In addition, ECP was also used as a part of calcineurin inhibitor (CNI) sparing protocols to reduce drug side effects such as nephrotoxicity, and neurological or infectious complications[43].

In KT, there are only a few reports available on the use of ECP in recurrent or refractory acute rejection after the failure of standard immunosuppression and in antibody-mediated chronic rejection (AMCR), but they have encouraging preliminary results[44]. Finally, ECP was also employed as a preventive treatment in a small case

series with a favorable outcome: Rejection did not occur in any of the treated patients, and the authors described a notable increase in circulating Tregs[45].

INDICATIONS FOR TA IN KT

Desensitization in ABO-incompatible KT

ABO blood group incompatibility is the first and most significant immunological barrier to a successful transplantation and for a long time has been a contraindication to KT. Hyper acute rejection or AMR in nondesensitized ABO-incompatible (ABO-i) KTs occurs due to the presence of circulating preformed antibodies against the blood group antigens A and B (isohemagglutinins), which are strongly exposed on the surface of endothelial cells and kidney parenchymal cells[46]. However, ABO-i KT was first attempted in the 1970s using A2 donors for recipients of blood groups O and B with only regular immunosuppression[47]. This was possible because, compared to blood group A1 and blood group B individuals, the A2 antigen is less reactive with isohemagglutinins and is expressed in lower amounts on the surface of red blood cells and tissue cells[48]. As experience increased, it became clear that low initial anti-A2 antibody titers in the recipient (IgG ≤ 1:2) were a requirement for the transplantations to be successful from an ABO A2 donor, significantly restricting the number of possible candidates[48-51].

To overcome the ABO barrier in KT and to increase donor pools, specific desensitization protocols have been refined to achieve a depletion of preformed antiA and/or antiB antibodies and the modulation of Bcell immunity[52]. In this context, the use of TA techniques represents a cornerstone of current desensitization protocols.

In the early days of ABO-i KT, Alexandre *et al*[53] introduced an effective desensitization protocol based on plasmapheresis and splenectomy. Subsequently, splenectomy was progressively replaced by the anti-CD20 antibody rituximab (RTX) due to the surgical risk and increased risk of sepsis. Initially, RTX has been used in combination with DFPP and splenectomy in 2002[54], while the first report of the use of RTX instead splenectomy came from Karolinska University Hospital in 2003[55]. In this protocol, in combination with RTX and conventional immunosuppression (tacrolimus, mycophenolate mofetil, and prednisolone), antigen-specific IA with a Glycosorb ABO column on pretransplant days - 6, - 5, - 4, and - 1[55]. After transplantation, three more IA sessions were performed every third day. Moreover, if there was a significant increase in the antibody titers, more sessions were added[55].

In contrast to the Swedish protocol[55], Wilpert *et al*[56] adopted an on-demand strategy for postoperative IA. Instead of scheduling pre-emptive posttransplant IA, they submitted patients to IA if their antibody titers were higher than 1: 8 in the first postoperative week and higher than 1: 16 in the second postoperative week, without any additional risk for the patients[56].

Ishida *et al*[57], in a retrospective cohort of 191 ABO-i KT recipients without postoperative administration of any prophylactic treatment for rejection, found no correlation between levels of antibody rebound and the incidence of AMR, even with antibody titers higher than 1: 64. The authors concluded that no treatment is necessary for rebounded anti-A/B antibodies as there is an immunological accommodation for elevated titers[57]. In fact, immunological accommodation is established early (2 wk) after successful KT and could explain the resistance to AMR despite the rebound of anti-A/B antibodies in the recipient[58]. The exact mechanisms of accommodation remain to be elucidated, although several have been proposed[59]. Similar results have been reported by previous studies[34].

In contrast, a group from Johns Hopkins reported that the incidence of AMR was significantly higher in recipients with high postoperative titers (≥ 1:64), but the clinical significance was variable, as there was no consistent clinical correlation for AMR[60]. The authors hypothesized that postoperative TPE could be helpful in preventing the rebound of anti-A/B titers until tolerance or accommodation occurs[60].

Consequently, the utility of postoperative antibody monitoring and prophylactic apheresis appears unclear and controversial. The transplant community should conduct larger studies with sufficient statistical power and with uniform and validated antibody titer measurements to find appropriate answers to this delicate issue.

Currently, cTPE is the preferred antibody removal strategy in the United States; membrane separation use is widespread in Japan, while IA is frequently practiced in Europe because of its safety and efficacy[58].

In many protocols, the number of pretransplant apheresis sessions is scheduled according to baseline antiA/B antibody titers[61,62]. Typically, on the day of transplantation, the target for an antibody level is ≤ 1:8 regardless of the applied TA

because higher levels have been correlated with a higher incidence of AMR[63]. However, the choice of TA technique could also be scheduled according to baseline antibody titers. In fact, the Guy's Hospital ABO-i desensitization regimen introduced such a desensitization scheme tailored to initial antibody titers[64]. In patients with baseline titers of ≤ 1:8, apheresis treatment was omitted, while RTX was not applied in patients with titers < 1:16[64]. DFPP was used in those with titers between 1:16 and 1:64 and antigen-specific IA (glycosorb-ABO IA columns) was used in those with titers above 1:64[64]. The justification for the use of IA only for those patients with titers > 1:64 was that these patients were expected to require the highest number of sessions, and DFPP is notably correlated with a higher risk of bleeding[65]. Instead, DFPP was preferred in patients with titers between 1:16 and 1:64 because it is a less-expensive technique, and fewer cycles of antibody removal should not significantly alter coagulation parameters[64]. The exact number of apheresis sessions depended on the course of the titers[64]. In conclusion, tailoring the intensity of desensitization treatment according to individual immunological risk should be the recommended strategy.

Desensitization in patients with preformed HLA-antibodies

Preformed anti-HLA antibodies represent another major immunological barrier to a successful KT. Sensitization occurs when the transplant candidate develops immunological memory to the donor's antigens from prior transplants, blood transfusions, and pregnancies[66,67]. Approximately 30% of the KT candidates have detectable anti-HLA antibodies and approximately half of them are "highly" sensitized with HLA antibody reactivity to over 80% of potential donors (panel reactivity antibody ≥ 80%)[68].

KT with donor-specific anti-HLA antibodies (DSAs) at pretransplant is known as HLA-incompatible transplantation. After transplantation, DSAs in high amounts cause hyperacute rejection, while in small amounts they reduce the survival of the graft by causing acute AMR and/or chronic humoral rejection[69,70]. As such, highly sensitized candidates present difficulties in finding a cross-match-negative kidney, and waiting on the list for an acceptable match may be exhausted. According to Fuggle *et al*[71], sensitized candidates remain on the waiting list for a compatible donor kidney two to three times longer than nonsensitized KT candidates. The possibilities for the highly sensitized candidate that is waiting on the deceased-donor transplant list are higher after a desensitization protocol and even better in those with an available living donor. In this context, TA has a central role as an anti-humoral therapeutic strategy.

Desensitization of deceased donor kidney transplant recipients: Current desensitization protocols commonly use a combination of high-dose intravenous immunoglobulin (IVIG) and RTX to lower the titers of preformed HLA-antibodies in candidates on the waiting list and increase the chances of finding an acceptable deceased-donor[72]. Moreover, TA (TPE or IA), if performed while on the waiting list, has historically been shown to reduce the long waiting times in highly sensitized candidates[29,73,74]. Such strategies, however, are not always effective and may produce risks correlated with extended immunosuppression on dialysis.

Regarding the efficacy of HLA antibody reduction, in preventing hyperacute rejection, acute AMR and later transplant glomerulopathy, by peri-pretransplant TPE in deceased-donor KT (DDKT), the available data are limited[75-77]. Beimler *et al*[75] reported for the first time a successful DDKT in two cross-match-positive recipients with a single peri-pretransplant TPE session and RTX. Cold ischemic time (CIT) due to the therapeutic protocol was not prolonged because TPE was performed during the transport of the kidneys from the donor center to the transplant center. After desensitization, the cross match turned negative, and TPE sessions were extended during the posttransplant period until stable allograft function was achieved to avoid an early rebound of DSAs[75]. Both patients showed good graft outcomes two years after KT[75]. Using the same desensitization protocol, the same group reported excellent short- and medium-term outcomes in a larger cohort of 12 DDKTs with positive cross matches, which turned negative after desensitization[76]. Recently, a retrospective cohort study of DSA-positive recipients who received DDKT showed that a single peri-pretransplant TPE session, in combination with anti-human thymocyte globulin (ATG) as induction immunosuppression, did not result in a lower incidence of acute AMR within 6 mo in comparison with the DSA-positive recipients who did not receive a TPE session[77]. Posttransplant TPE was not performed because the protocol included 3 to 5 d of ATG induction[77].

Loupy *et al*[78], from the Paris group, reported the results of a combined posttransplant prophylactic IVIg/RTX/TPE treatment in DDKT with preformed DSAs but a negative cross match on the day of transplant. The patients received 9 TPE sessions on an alternate-day basis at posttransplant plus IVIg 2 g/kg at days 0, 2, 42,

and 63 and RTX on days 2 and 22. At 1-year posttransplant, patient and graft survival rates and the rate of acute AMR were comparable between the patients who received only IVIg and those who also received RTX and TPE. However, the estimated glomerular filtration rate (e-GFR) was significantly worse, and proteinuria was significantly higher in the IVIg group, as well as the rate of chronic AMR[78]. These differences in long-term function were characterized by a significant decrease in the DSA mean intensity of fluorescence (MFI), as detected with the Luminex solid phase immunoassay, in the group of patients receiving the more intensive post transplant prophylactic regimen in comparison with the IVIg group[78]. Recently, the Paris group reported the long-term results of a high immunological risk program including patients with high peak DSA levels (MFI > 3000) and a negative cross match at transplantation day who received a posttransplant desensitization protocol with high-dose IVIg, TPE and RTX. The results were compared to a control group including patients with a lower immunological risk (MFI between 500 and 3000) on transplantation day and in whom posttransplant desensitization was based on IVIg alone[79]. Patient survival was the same between the two groups. However, there were significantly more cases of acute T-cell rejection and AMR in the group with MFI > 3000, which clinically translated into significantly lower graft survival[79].

IA, aimed at preventing humoral graft injury, has also been used with mixed results. The Vienna transplantation center reported a favorable allograft outcome in a series of highly sensitized kidney transplant recipients after a peri-pretransplant IA session with a staphylococcal protein A column supplemented by repeat posttransplant treatment[80]. Subsequently, the same group described that a single peri-pretransplant IA, in addition to pre-emptive ATG, can turn a positive cross match into a negative cross match, enabling a successful DDKT supported by a favorable long-term graft survival at 3 years[81]. The authors confirmed these data by extending their initial experience in a later paper[82]. Repeated posttransplant IA sessions have been performed in this protocol to prevent a potentially harmful rebound of DSAs[81,82]. In line with the Vienna group, Higgins *et al*[83], in a previous study, reported a cohort with a successful cross-match conversion and prevention of hyper-acute rejection by peri-pretransplant IA treatment. However, in this case, a considerably high graft loss rate was observed during follow-up, with only 54% of transplants surviving after a median follow-up of 26 mo[83]. The difference in the outcome between these studies could be explained by the significant differences between the desensitization protocols. Unlike the Vienna group[81,82], Higgins *et al*[83] did not repeat post-transplant IA sessions. In addition, the Vienna group[81,82], to obviate an exaggerated increase of CIT, excluded transplantation for patients in whom a negative cross match could not be obtained by treatment with 6 L of plasma, while Higgins *et al*[83] in some patients prescribed more than 30 L plasma volume to convert a positive cross match, which resulted in significant increases in CIT (up to 62 h). However, the Vienna group recently reported that one-third of 101 DSA-positive recipients of DDKT underwent intense IA-based desensitization and experienced acute AMR and that DSA MFI levels were significantly associated with acute rejection (20 *vs* 71% AMR rates at < 5000 *vs* > 15000 peak DSA MFI)[84]. The 3-year graft-survival rate in DSA-positive recipients was significantly lower than that of the DSA-negative recipients (79% *vs* 88%; $P = 0.008$)[84].

These data highlight that MFI levels have significant prognostic value and suggest that the intensification of TA treatment in posttransplant desensitization protocols must be personalized according to MFI levels.

Desensitization of living-donor kidney transplant recipients: For sensitized candidates with an available but incompatible living donor, paired donor exchange (PDE) is the best alternative option. However, for most highly sensitized candidates, the chance of finding a match in the relatively small pools of donors in PDE programs is reduced, and desensitization alone or desensitization in combination with PDE present almost the only viable option for transplantation[85]. HLA-incompatible desensitized living-donor KT (LDKT) *vs* HLA-compatible LDKT has significantly lower graft survival[86]. Multicenter study results indicate, however, that it is worth desensitizing HLA-incompatible patients who have a potential living donor, as after KT these patients have significantly better long-term survival than highly sensitized candidates on a KT waiting list who did not receive a kidney from a deceased donor[87-89].

TA has a central role in current desensitization protocols. The most commonly used protocol is a combination of alternate-day TPE followed by low-dose IVIg (100-150 mg/kg) prior to transplantation[87-91]. Most transplant centers also initiate antirejection medications, tacrolimus, and mycophenolate mofetil (MMF), up to 2 wk prior to surgery[92]. Montgomery *et al*[87], in the largest series of HLA desensitization based on TPE plus low-dose IVIg, at the 5-year follow-up, showed a significantly greater

survival in patients who received LDKT (90.6%) than in those who remained on dialysis (51.5%) or in those placed on a DDKT wait list with or without KT (65.6%). On average, patients received 4 ± 4 TPE treatments before LDKT and 5 ± 4 TPE treatments after LDKT[87]. More recently, Orandi *et al*[88], in a larger multicenter (n = 22) United States study that involved 1025 patients, validated the results from the Baltimore group[87]. Gloor *et al*[93] , to overcome a positive cross match in 14 LDKT recipients added RTX and splenectomy to the protocol TPE/low-dose IVIg in an attempt to decrease the high AMR rate.

However, a 43% AMR rate was detected, while the patient and graft survival rates were 86% and 78%, respectively at 15 mo. Magee *et al*[94] reported their experience with TPE/low-dose IVIG plus RTX in 28 cross-match-positive patients. The AMR rate was high (39%), but within a mean follow-up of 22 mo, the mean serum creatinine level was good (1.5 mg/dL), and only 3 grafts were lost. Similar results, applying TPE/low-dose IVIg plus RTX, have been reported by the University of Illinois in 51 transplanted patients[95]. The acute rejection rate was 33%, with optimal graft survival at 2 years (93%).

Morath *et al*[96] examined the effect of adding one dose of RTX (375 mg/m^2) just prior to KT with IA performed before and after transplantation. After a median of 10 IA treatments, all ten patients were desensitized successfully and transplanted. The recipients also received a median of 7 posttransplant IA treatments. After a median follow-up of 19 mo, the reversible AMR rate was 30%, and the patient and allograft survival rates were 100% and 90%, respectively, with a mean serum creatinine level of 1.6 mg/dL[96]. Similar results with RTX plus IA have been reported recently by Kauke *et al*[97] on a small series of 8 LDKT recipients. Klein *et al*[98], on a series of 23 sensitized patients, performed pretransplant IA sessions plus tacrolimus, MMF, and steroids, with the goal of achieving an MFI < 1000 on transplantation day. On days 0 and 1, recipients also received one dose of RTX. The induction therapy was based on either ATG or basiliximab, and IA sessions were maintained posttransplantation until serum creatinine became < 2 mg/dL and MFI was stable at < 1000. This desensitization protocol showed excellent results at the 2-year follow-up, with a graft survival rate of 100% and a median serum creatinine level of 1.42 mg/dL[98]. To allow LDKT in 6 highly sensitized patients, Rostaing *et al*[99] performed an IA-based desensitization protocol plus IVIg, RTX, and ATG as induction therapy. This protocol effectively reduced or eliminated DSAs in 71% of recipients at the time of transplant. Three recipients manifested an AMR, but long-term renal function was good.

Woodle *et al*[100] in an alternative protocol incorporating TPE, the proteasome inhibitor bortezomib, and RTX, showed a significant decrease in DSAs in both LDKT and DDKT with successful transplantation in 19 of 44 highly sensitized patients and low acute rejection rates (18.8%) at 6 mo.

In a recent review, Malvezzi *et al*[101] proposed an algorithm based on MFI pretransplant levels for the use of the various TA techniques in desensitization protocols. In their experience, the authors suggest that the use of TPE should be restricted in cases where the highest pretransplant MFI is ≤ 9000. In such circumstances, TPE should be delivered on a daily basis until MFI becomes ≤ 3000. MFI must be assessed after every 5 sessions. If the MFI of the DSA is > 9000 but below 13000, DFPP can be implemented on a daily basis. When the target of MFI < 9000 is reached, DFPP can be converted to TPE. In the event that MFI is > 12000 before starting desensitization, IA has to be applied on a daily basis. When the MFI is reduced (*i.e.*, < 6000), IA can be replaced by DFPP or TPE to obtain an MFI threshold of about 3000. The authors conclude that in all of these scenarios, as soon as MFI is reduced to < 3000, KT can be performed as in this case DSA strength is low. In our opinion, based on current studies, the best strategy is to apply TA, preferably IA, plus RTX until MFI becomes < 3000. The addition of IVIG might also be relevant in this setting.

Antibody-mediated rejection

Antibody-mediated rejection (AMR) is a severe complication after KT with potentially deleterious effects on graft survival. Currently, AMR is widely recognized as a continuous process with varying degrees of activity and damage, clinically and histologically, expressed with multiple phenotypes, now identified as acute AMR, subclinical AMR, and chronic AMR[102,103].

Despite the use of desensitization protocols, up to one-third of highly sensitized recipients may develop AMR following transplantation[104,105]. Hence, the ability to successfully deliver incompatible transplants and optimize long-term results is contingent on the ability to successfully approach and manage an AMR. AMR is also of significant burden in non-sensitized individuals, as *de novo* DSA (dnDSA) can emerge early or late following KT[106].

Early acute AMR can be severe and result in graft loss, but it is also potentially

responsive to current treatments[103]. Instead, late acute AMR (more than 6 months posttransplant), can be a mixed cellular and humoral rejection, and it is often nonresponsive to current treatments, such as chronic AMR and, in some cases, subclinical AMR. Late acute and chronic AMR may result from dnDSA formation, the incomplete elimination of DSA following an earlier acute AMR episode, or the persistence of preformed DSA after desensitization[103]. TA, as an adjunctive therapeutic option, has a central role in the treatment of AMR.

TA and IVIG: When acute AMR occurs, TPE or IA plus IVIG and increased immunosuppression is considered the current standard of care (SOC) treatment, as it can be used to decrease antibody levels and arrest the rejection process in the majority of patients[103].

In a recent meta-analysis, Wan *et al*[107], regarding graft survival after antibody removal with TPE or IA, based on 5 RCTs, showed no benefit in the trials with a shorter follow-up (1-7 mo)[108,109], while those with a longer follow-up (2-5 years) showed a trend towards a benefit[28,110,111].

In a recent retrospective cohort study investigating TPE plus IVIG in late AMR, with approximately 50% of patients having chronic histology lesions, Lee *et al*[112] showed an improvement of graft survival in the intervention group compared to the control group who did not receive any therapy, in a mean follow-up of 7 years. In contrast, Einecke *et al*[113] observed no effect on graft survival after treatment with TPE plus IVIG in late AMR, with approximately 63% of patients having chronic histology lesions.

In conclusion, based on current data, the basis of establishing TPE plus IVIG as SOC treatment in AMR is lacking strong evidence, and a high-quality RCT with sufficient power to evaluate the efficacy of this treatment would provide reassurance on this delicate topic. However, it is extremely improbable that such a trial will be conducted due to the ethical perplexity of enrolling patients to a no-treatment group, which is historically related to high risks of graft failure.

Add-on treatments to TA and IVIG: Different add-on treatments in the current SOC treatment have been proposed over time per transplant center preference[103,107].

The use of RTX in acute AMR showed promising results in several small retrospective series[114,115]. In the first controlled trial using RTX plus TPE/IVIG *vs* IVIG alone, Lefaucheur *et al*[116] concluded that high-dose IVIG is inferior to combination therapy. However, in this trial, it was impracticable to determine which of RTX or TPE led to the improvement[116].

In addition, 2 retrospective cohort studies compared RTX plus TPE/IVIG to TPE/IVIG or IVIG alone, and both showed an improvement in graft survival in the RTX group[117,118]. The patients in the RTX group, however, received a higher dose of TPE and IVIG, limiting the ability to make a direct comparison between groups.

In a small multicenter double-blind RCT comparing RTX plus TPE/IVIG to placebo plus TPE/IVIG for the treatment of acute AMR, Sautenet *et al*[119] showed no additional benefit from RTX in graft survival after 1 year. However, the 1-year follow-up period may not have been long enough to identify a difference in graft survival. Recently, Oblak *et al*[120], with the limitations that a retrospective cohort study can provide, confirmed no evidence of any benefit in adding RTX to SOC treatment for AMR in a longer follow-up period (2 years).

Bortezomib, a proteasome inhibitor, in several nonrandomized retrospective studies and case reports, showed benefit to treat acute AMR in combination with TPE and IVIG[121,122] or TPE and RTX[123], while other studies have shown no improvement in e-GFR after bortezomib when used as add-on therapy with TPE and IVIG for late AMR[124].

The single RCT comparing the use of bortezomib, in patients with mixed AMR and acute cellular rejection, in conjunction with TPE and ATG *vs* TPE, RTX, and ATG or TPE and ATG alone, showed no difference in graft survival between the 3 groups[125].

The complement inhibitors eculizumab, a humanized monoclonal IgG antibody that binds to complement protein C5 and inhibits the formation of MAC, and C1-INH, a serine protease inhibitor that inactivates both C1r and C1s, inhibiting in this way the first step of the complement cascade, have also been evaluated in combination with TPE and IVIG in the treatment of AMR.

Locke *et al*[126] reported the first case report on the use of eculizumab in combination with TPE and IVIG to treat severe AMR, demonstrating a reversal of the AMR episode. In a study of 24 patients who developed severe oliguric AMR after HLA-incompatible LDKT, Orandi *et al*[127] showed that a combination of splenectomy plus eculizumab and RTX as an add-on therapy to TPE/IVIG resulted in an effective intervention for rescuing and preserving allograft function in comparison with splenectomy alone or eculizumab alone as an add-on therapy.

In an RCT in which 18 patients with acute AMR were assigned to C1-INH (Cinryze) plus TPE/IVIG or placebo plus TPE/IVIG, Montgomery *et al*[128] showed less transplant glomerulopathy at 6 months in the C1-INH group. A multicenter phase III RCT (NCT02547220) evaluating C1-INH as an add-on therapy to TPE/IVIG or IA/IVIG has just concluded, and we are waiting for the results to be published.

In conclusion, various add-on treatment options are employed for the current SOC treatment based on their targets in the steps of AMR pathogenesis with different results. Future RCTs should assess definitive endpoints, and until then, the regimen to be used should be considered on a case-by-case basis.

ECP: There are only a few reports available on the use of ECP in chronic AMR. Sunder-Plassman *et al*[129] employing intensive and long term ECP treatments (2 consecutive procedures every 2 wk for 17 cycles), showed a benefit in treating a single patient with chronic rejection. Dall'Amico *et al*[130] reported progressive improvement in renal function and consecutive biopsy specimens during the course of ECP in treating one patient with chronic rejection. In contrast, Horina *et al*[131] showed no response in treating two patients with two consecutive ECP procedures per month for 3 mo. Further experience on the usefulness of ECP in AMR is required.

Recurrence of primary focal segmental glomerulosclerosis

Approximately 30% of cases of primary focal segmental glomerulosclerosis (FSGS) recur after first KT and are associated with early graft loss in up to 50% of patients[132]. The prediction of recurrence is even higher than 75% in subsequent grafts when the first graft has been lost because of recurrence[133].

Primary FSGS seems to be induced by a circulating factor that targets podocytes. Several candidates have been suggested, although until now, the specific factor(s) involved remain unknown[134]. Recently, Delville *et al*[135] identified a panel of seven antibodies (CD40, PTPRO, CGB5, FAS, P2RY11, SNRPB2, and APOL2) that predict posttransplant FSGS recurrence with 92% accuracy. The pretransplant elevation of anti-CD40 antibody alone had the best correlation (78% accuracy) with recurrence of FSGS after transplantation[135]. In addition, anti-CD40 antibodies purified from patients with FSGS recurrence have been proven to be particularly pathogenic in human podocyte cultures[135].

TPE or IA with either a protein A or anti-IgG column have been used with benefit, alone or in combination with cyclophosphamide, with the scope to remove the putative circulating permeability factor[136-140]. Dantal *et al*[140] showed that the administration to rats of material eluted from protein A columns from patients with disease recurrence after KT increased the urinary albumin excretion.

In a literature review, Ponticelli[141] reported that approximately 70% of children and 63% of adults with recurrent FSGS receiving TPE or IA achieved complete or partial remission of proteinuria. Similar data have been reported in two recent meta-analyses[142,143].

The duration and frequency of TPE sessions are not yet unanimously agreed upon. A typical TPE regimen is 1.5 plasma volume exchanges for three consecutive days and then every other day for a total of two weeks[132].

TPE has also been used as an adjunctive treatment to other immunosuppressive agents. Canaud *et al*[144], in a series of 10 patients, reported good results by combining intravenous cyclosporine with high-dose steroids, mycophenolate, and frequent TPE sessions slowly tapered down for nine months.

In the last ten years, the use of RTX in recurrent FSGS has rapidly expanded with beneficial effects[145,146]. In addition to being a selective depleting agent of B-lymphocytes, RTX seems to have a direct protective effect on podocytes. RTX is able to protect sphingomyelin phosphodiesterase acid-like 3b (SMPDL-3b) and acid sphingomyelinase (ASMase) by binding to SMPDL-3b, a protein exposed in podocyte lipid rafts that may be the target of the permeability factor of FSGS and that displays a sequence identified by RTX[147,148]. RTX, in combination with TPE, seems to have better efficacy, as suggested by case reports[149,150]. Other immunosuppressive agents, such as abatacept and antiTNFα agents, have shown prominent results in recurrent FSGS[151,152], but the experience of these agents in combination with TPE is inexistent.

Other indications of TA in KT

Complement-mediated atypical hemolytic uremic syndrome: Complement-mediated atypical hemolytic uremic syndrome (aHUS) is a rare disease that results from genetically determined complement deregulation with an alternative pathway of activity secondary to either loss-of-function mutations in regulators [factor H, factor I, and membrane cofactor protein (MCP)] or gain-of-function mutations in activators (C3 and factor B) of the alternative pathway[153]. In addition, complement-mediated aHUS may result from autoimmune mechanisms, including the development of auto

antibodies to complement proteins[153]. Mutations in factors H, factor I, factor B, and C3 have a high risk of recurrence (75%), and more than 90% of those with recurrence are strongly associated with graft failure, typically within the first year, because the altered proteins persist in the blood after KT[154]. In contrast, mutations of MCP are associated with a recurrence rate of only 20% and considerably more favorable graft survival rates because kidney transplants express normal proteins[155].

TPE can remove auto-antibodies against complement proteins or mutated circulating complement regulators while replacing absent or defective complement regulators and has been used in regimens for the prevention of recurrence, prior KT, and the recurrence of complement-mediated aHUS posttransplantation with relatively poor response to treatment[156]. The introduction of eculizumab, an anti-C5 monoclonal antibody, has favorably changed the outcomes and challenged the role of TPE in the treatment of aHUS.

The added therapeutic benefits ofTPE in a pre-emptive prophylactic protocol with eculizumab prior to KT, used by some centers[157], remain unclear and questionable. TPE remains an alternative therapeutic option only when eculizumab is not available in patients with anti-complement factor H antibodies and when thrombocytopenia is still present during the first days of eculizumab administration[158,159].

***De novo* thrombotic microangiopathy:** *De novo* thrombotic microangiopathy (TMA) after KT may be due to any of the etiologies that induce TMA in the general population. However, the most common causes of TMA among kidney transplant recipients include drug-induced TMA due to calcineurin inhibitors and mammalian target of rapamycin (mTOR) inhibitors, ischemia reperfusion injury, AMR, and viral infections[160].

If switching to a different immunosuppressive regimen or if the treatment of underlying infection does not lead to a resolution of signs and symptoms of TMA and there is a clinical deterioration, TPE can be attempted to improve the course of the disease and subsequent graft damage[161], although the level of evidence is low. If available, eculizumab is the treatment of choice in these cases[162,163].

In AMR-associated TMA, improved outcomes have been reported with TPE and IVIG therapy[164]. Eculizumab is the recommended treatment in AMR-associated TMA if hemolysis persists despite maximal management with TPE and in those with TPE dependency[160].

Antiphospholipid syndrome and systemic lupus erythematosus: The antiphospholipid syndrome (APS) is a multisystem autoimmune disorder characterized clinically by thrombotic episodes in the arterial or venous circulation, and serologically by the persistent evidence of antiphospholipid antibodies (aPL). APS occurs either as a primary condition or secondary in the setting of an underlying systemic autoimmune disease, mainly systemic lupus erythematosus (SLE)[165]. The kidney is one of the organs that can be compromised by occlusion of a broad spectrum of renal blood vessels, ranging from glomerular capillaries to the main renal artery and vein[165].

Early graft arterial or venous thrombosis, or TMA, remains the most frequent cause of renal graft failure in patients with APS[166]. In addition, several studies have found that patients on maintenance hemodialysis, and consequently a substantial number of renal transplant recipients have a high prevalence of circulating aPL, which can damage the allograft[167,168]. Treatment of APS with long-term warfarin for arterial or venous thrombosis is recommended after renal transplantation and most transplant nephrologists prefer to inhibit the coagulation system in all patients with aPL and a history of coagulation events during the peritransplant period[169,170]. However, anticoagulation therapy increases the risk of bleeding complications, which may lead to early graft loss, and graft thrombosis takes place in 40% of the APS population despite anticoagulant therapy[171].

Prophylaxis with TPE for antibody removal, in addition to full anticoagulation therapy, before living-donor KT has been reported effective in one patient with primary APS[172] and in one patient with secondary APS in the setting of SLE[173]. However, in case of catastrophic APS (CAPS), which is characterized by diffuse TMA (vascular occlusions involving three or more organ systems)[174], prophylactic administration of eculizumab to prevent recurrence of CAPS after KT should be considered the preferred therapeutic option as have been used with success in one patient together with continuous systemic anticoagulation and standard immunosuppression[175].

Barbour *et al*[166] reported a case of acute recurrence of TMA after KT, in a patient with APS and lupus nephritis successfully treated with TPE albeit with some irreversible graft damage and renal impairment. These results suggest that further studies are warranted.

Recurrent and *de novo* anti-glomerular basement membrane disease: The histological recurrence of anti-glomerular basement membrane disease (GBM) may be as high as 50% in patients who receive a transplant while circulating anti-GBM antibodies persist[176,177]. However, there are only a limited number of documented cases of symptomatically recurrent anti-GBM disease, as most patients are asymptomatic[176].

De novo anti-GBM disease is seen in up to 15% of transplant recipients with Alport syndrome who develop anti-GBM antibodies to a collagen component [alpha5 (IV) NC1] carried by the transplanted kidney that is lacking in Alport patients[178]. The approach to the treatment is the same as in the native kidneys. TA should be used promptly to remove the causative antibody plus glucocorticoids and cyclophosphamide to inhibit further autoantibody production[177]. IA and TPE have comparable outcomes[179,180]

Recurrence of antineutrophil cytoplasmic antibody-associated vasculitis: The relapse of antineutrophil cytoplasmic antibody-associated vasculitis in KT patients is a rare event. In a recent review of 11 studies, including 441 patients, the relapse rate was 10%[181].

In the case of a recurrence, the treatment options for remission induction are similar to those of nontransplanted patients. Both cyclophosphamide- and RTX- based induction regimens have shown effectiveness in the treatment of posttransplant relapses[182].

TPE is recommended, in conjunction with glucocorticoids and either cyclophosphamide or RTX in the setting of relapse manifesting as alveolar hemorrhage, severe segmental necrotizing glomerulonephritis with serum creatinine above 4.0 mg/dL, and concurrent anti-GBM disease[182-184].

CONCLUSION

The application of TA in KT is currently a cornerstone of therapy for several clinical conditions, such as in desensitization protocols for ABO-i KT and in patients with preformed HLA-antibodies, in the treatment of AMR, and with the recurrence of different glomerulopathies after KT as in recurrent primary FSGS. However, strong evidence is scarce, and more clinical researches, with a high standard of quality RCTs, are demanded to establish the use of each TA method for the clinical problems that occur in KT.

In addition, in the era of new and emerging biological immunosuppressive therapies with an increasing number of specific actions and immune targets directed against cell-surface antigens or plasma-soluble molecules, the use of TA, and the optimal timing and dose, as an adjunctive therapeutic option becomes challenging in the study of future therapeutic protocols, which will best address open issues for better clinical outcomes.

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ORIGINAL ARTICLE

Retrospective Study

Histopathological characteristics and causes of kidney graft failure in the current era of immunosuppression

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Abstract

BACKGROUND

The histopathological findings on the failing kidney allograft in the modern era is not well studied. In this study, we present our experience working with kidney transplant recipients with graft failure within one year of the biopsy.

AIM

To report the histopathological characteristics of failed kidney allografts in the current era of immunosuppression based on the time after transplant, cause of the end-stage renal disease and induction immunosuppressive medications.

METHODS

In a single-center observational study, we characterized the histopathological findings of allograft biopsies in kidney transplant recipients with graft failure within one year after the biopsy.

RESULTS

We identified 329 patients with graft failure that met the selection criteria between January 1, 2006 and December 31, 2016. The three most common biopsy findings were interstitial fibrosis and tubular atrophy (IFTA, 53%), acute rejection

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(AR, 43%) and transplant glomerulopathy (TG, 33%). Similarly, the three most common causes of graft failure based on the primary diagnosis were AR (40%), TG (17%), and IFTA (13%). Most grafts failed within two years of post-transplant (36%). Subsequently, approximately 10%-15% of grafts failed every two years: > 2-4 years (16%), > 4-6 years (13%), > 6-8 years (11%), > 8-10 years (9%) and > 10 years (16%). AR was the most common cause of graft failure in the first six years (48%), whereas TG was the most prevalent cause of graft failure after 6 years (32%) of transplant.

CONCLUSION
In the current era of immunosuppression, AR is still the most common cause of early graft failure, while TG is the most prevalent cause of late graft failure.

Key words: Kidney biopsy; Acute rejection; Graft failure; Transplant glomerulopathy; Interstitial fibrosis and tubular atrophy

Core tip: There have been significant improvements in early graft survival. However, long-term graft survival has only had modest improvement. Causes of "true" late kidney allograft failure remain unclear. In this study, we explored the causes of graft failure based on the various factors, which may allow providers to determine interventions to prevent poor outcomes. We found, acute rejection, mainly antibody-mediated rejection, was the most common cause of early graft failure. And transplant glomerulopathy was a common cause of late graft failure, which occurred mainly after 6-7 years post-transplant even surpassed acute rejection.

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INTRODUCTION

Kidney transplantation is the best form of treatment for patients with end-stage renal disease (ESRD) of any cause. Kidney transplant recipients (KTRs) experience survival benefits in all age groups have a better health-related quality of life and transplant is cost-effective compared to dialysis[1-3]. There have been significant improvements in early graft survival due to advances in immunosuppression and the overall medical care of transplant recipients. However, long-term graft survival has only had a modest improvement[4-6]. Allograft failure among transplanted kidney recipients is now the fourth leading cause of ESRD in the United States[7]. Studies from nearly a decade ago suggest that antibody-mediated rejection (ABMR) and disease recurrence are the most common causes of graft failure[7,8]. However, the causes of "true" late kidney allograft failure remain unclear[9]. In this study, we explored the causes of graft failure based on time after transplant, causes of ESRD and induction immunosuppressive medication in the current era, which may allow providers to determine interventions to prevent poor outcomes.

MATERIALS AND METHODS

Study population and design

We study KTRs who were transplanted at the University of Wisconsin, and who had graft failure between January 1, 2006 and December 31, 2016 and transplanted between January 1, 1994 to December 31, 2016. We chose 2006 as a current era because at that time most of our clinical practice including histopathological reporting were protocolized. Patients were included if they underwent a kidney biopsy within one

year prior to the graft failure. If they had multiple biopsies within one year prior to the graft failure, the biopsy closest to the graft failure was included in the analysis. Patients with primary graft dysfunction (defined as not having functional allograft and needing dialysis for at least 3 mo post-transplant or graft nephrectomy) or death with a functional graft were excluded from the study (Figure 1). This study was approved by the Health Sciences Institutional Review Board at the University of Wisconsin.

Data collection

We analyzed data on age, gender, race, re-transplant status, the cause of ESRD, type of transplant, induction immunosuppression, organ failure method before graft failure (re-transplant *vs* initiation of dialysis). In cases where a patient had multiple biopsy diagnoses, all diagnoses were also reported separately, although the primary diagnosis (first diagnosis) was used for the cause of graft failure. We divided the causes of graft failure based on the post-transplant interval divided into 2 years interval, based on the causes of ESRD and also the types of induction immunosuppressive medication.

Immunosuppression

Patients undergoing kidney transplant received induction immunosuppression with either a depleting (anti-thymocyte globulin, alemtuzumab or OKT3) or non-depleting (basiliximab or daclizumab) agent-based on immunological risk factors. Patients were typically maintained on a triple immunosuppressive regimen with a calcineurin inhibitor (CNI, usually tacrolimus), antiproliferative agent (usually mycophenolate mofetil or mycophenolic acid), and steroids. Some patients had early steroid withdrawal based on clinical judgment and the patient's request. Doses and drug levels were individually adjusted at physician discretion based on the patient's clinical condition, including infection, malignancy, and rejection. Patients were maintained on the same immunosuppressive medication until graft failure. However, if there was a feature of CNI toxicity on biopsy, then CNI trough goal was lowered or even discontinued based on physician discretion. Once the patient return on dialysis, immunosuppressive medication was tapered down and maintained only on low dose steroid. Switching to mTOR inhibitor among failing graft was not common practice.

Kidney allograft biopsy

The majority of the biopsies were performed for-cause, mainly for the unexplained rise in serum creatinine, concern for rejections, significant proteinuria, or the development of *de novo* donor-specific antibodies (DSA). Protocol biopsies were performed at months 3 and 12 for all patients with pre-transplant DSA, and 6-12 wk after treatment of rejection.

Rejection treatment

ABMR treatment protocols at our institution are based on both the severity of rejection and the time after transplant at which ABMR is diagnosed as described previously[10]. Briefly, for early rejection (within 3 mo post-transplant), treatment includes dexamethasone 100 mg bolus and taper, plasmapheresis (PP) 4-6 sessions, and intravenous immunoglobulin (IVIG) 100 mg/kg after each PP. Late rejection (> 3 mo post-transplant) is treated with dexamethasone 100 mg bolus and taper and IVIG 200 mg/kg every 2 wk × 3. Rituximab 375 mg/m^2 as a single dose is added based on clinical and laboratory characteristics. The treatment regimen for both smoldering and clinical rejection is the same at our institution.

Treatment of acute cellular rejection (ACR) is also based on Banff criteria and severity. Borderline and Banff stage I rejection is treated with steroid pulse. Banff II and III ACR are treated with steroid pulse and Thymoglobulin 6-10.5 mg/kg in 4 to 7 divided doses. In mixed rejection, steroid pulse, IVIG, Thymoglobulin 10.5 mg/kg ± rituximab are used.

Statistical analysis

Continuous data were compared using Student's *t*-test or the Wilcoxon rank-sum test, as appropriate, while categorical data were analyzed using Fisher's exact test or chi-square test. P values < 0.05 were considered statistically significant. All analyses were performed using the MedCalc Statistical Software version 16.4.3 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016).

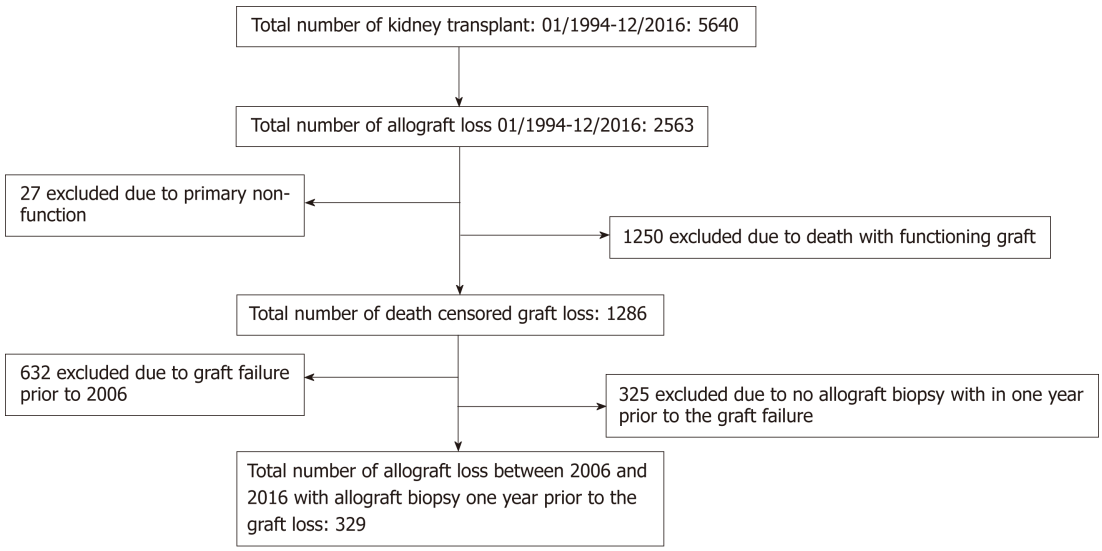

Figure 1 Study design: Death censored graft failure from 2006-2016 with allograft biopsy within one year prior to the graft failure.

RESULTS

Study population

A total of 654 patients had death-censored graft failure during the study period. Of these, 329 (50%) fulfilled our selection criteria and were included in the study.

Baseline characteristics

Out of the 329 KTRs included in the study, 127 (39%) were female and the majority were Caucasian (77%). Mean age at the time of transplant was 42.2 ± 13.7 years. Glomerulonephritis was the most common cause of ESRD and 33% were living KTRs. More than 50% had DSA around the time of graft failure. The mean interval from biopsy to graft failure was 106.5 ± 104.6 d (Table 1).

Biopsy findings

Interstitial fibrosis and tubular atrophy (IFTA) was the most common biopsy finding in 53% of all failed grafts, followed by acute rejection (AR) in 43% and transplant glomerulopathy (TG) in 33%. Less common findings were acute tubular necrosis, arteriosclerosis, recurrence of disease, donor vascular disease and BK nephropathy (BKVN) (Figure 2).

Common causes of graft failure based on the primary diagnosis

AR was the most common cause of graft failure and accounted for 40% (32% ABMR or mixed rejection and 8% ACR) of all graft failure. TG (17%), IFTA (13%), disease recurrence (7%) including the recurrence of diabetic nephropathy and glomerular disease, and BKVN (5%) were the following common causes of graft failure. Other less common causes of graft failure were donor vascular disease, prolonged acute tubular necrosis, CNI toxicity, and renal infarction (18% total graft failures). Among patients with AR as a cause of graft failure, 74 % had human leukocyte antigen (HLA) DSA at time of a biopsy, while 17% did not have HLA DSA and in 9% HLA DSA was not tested (Figure 3).

Common causes of graft failure based on the cause of ESRD

We further analyzed the cause of graft failure based on the three most common causes of ESRD: Glomerulonephritis, diabetes, and hypertension. AR was significantly higher in the glomerulonephritis and hypertension group compared to diabetes, and acute tubular necrosis was higher in the hypertension group (Table 2).

Common causes of graft failure based on the induction immunosuppressive medication

Patients were divided into two groups based on the induction immunosuppressive medication they received at time of transplant: Depleting agents (Anti-thymocyte globulin or alemtuzumab or OKT3) and non-depleting agents (basiliximab or daclizumab), which also included patients who received no or unknown induction. In the non-depleting group, TG was a significantly higher cause of graft failure

Table 1 Baseline characteristics, *n* (%)

Baseline characteristics	
Total number of graft failure	329 (100)
Female gender	127 (39)
Mean age at the time of transplant (yr)	42.2 ± 13.7
Caucasian	253 (77)
Causes of end stage renal disease:	
Glomerulonephritis	99 (30)
Diabetes	71 (22)
Hypertension	35 (11)
Polycystic kidney disease	34 (10)
Congenital disorder	9 (3)
Other	81 (25)
Mean number of transplants (Range 1-3)	1.29 ± 0.59
Living donor transplant	108 (33)
Induction Immunosuppression:	
Basiliximab	179 (54)
Thymoglobulin	52 (16)
Alemtuzumab	66 (20)
Other	32 (10)
Organ failure method:	
Resumption of dialysis	319 (97)
Re-transplantation (preemptive re-transplant)	10 (3)
DSA within a year prior to the graft failure:	
Present	184 (56)
Absent	89 (27)
Not tested	56 (17)
Mean graft survival (yr)	4.9 ± 4.4
Mean interval between biopsy and graft failure (d)	106.5 ± 104.6

DSA: Donor-specific antibodies.

compared to depleting agent group 48% *vs* 24% (Table 3).

Causes of graft failure according to time after transplant

AR, was the most common cause of graft failure in the early post-transplant period (within six years post-transplant) and accounted for 31% of total graft failures. (23% ABMR or mixed rejection and 8% ACR). There was a significant trend for graft failure due to rejection in the early post-transplant period ($P = 0.001$), while in the late post-transplant period, TG was the most common cause of graft failure ($P \leq 0.001$). The incidence of graft failure due to AR was higher up to 6 years post-transplant, with TG being the most common cause after 6 years (Figure 3). A total of 101 (48% of 212) graft failures within six years post-transplant were due to AR compared to 31 (26% of 117) after six years post-transplant ($P = 0.01$). TG was the primary cause of graft failure in 9% of patients within the first six years compared to 32% after six years ($P < 0.001$) (Figure 4). Rejection, TG, IFTA, and disease recurrence were evenly distributed as primary causes of graft failure after 10 years, each at approximately 20%-25%. Unsurprisingly, BKVN was more common in first 4 years post-transplant.

The most common time for graft failure was within two years post-transplant ($n = 117$, 36%). Subsequently, approximately 10%-15% of grafts failed every two years: > 2-4 years ($n = 51$, 16%), > 4-6 years ($n = 44$, 13%), > 6-8 years ($n = 35$, 11%), > 8-10 years ($n = 31$, 9%) and > 10 years ($n = 51$, 16%). Among 56 (17%) patients with the primary diagnosis of TG as a cause of graft failure, 25 (45%) had at least one episode of ABMR in the past. Similarly, around the time of last biopsy (± 3 mo), HLA-DSA was present in 30 (54%), DSA was not detected in 13 (23%) of the patients, and in 23% DSA was not checked around the time of biopsy (Figures 4 and 5).

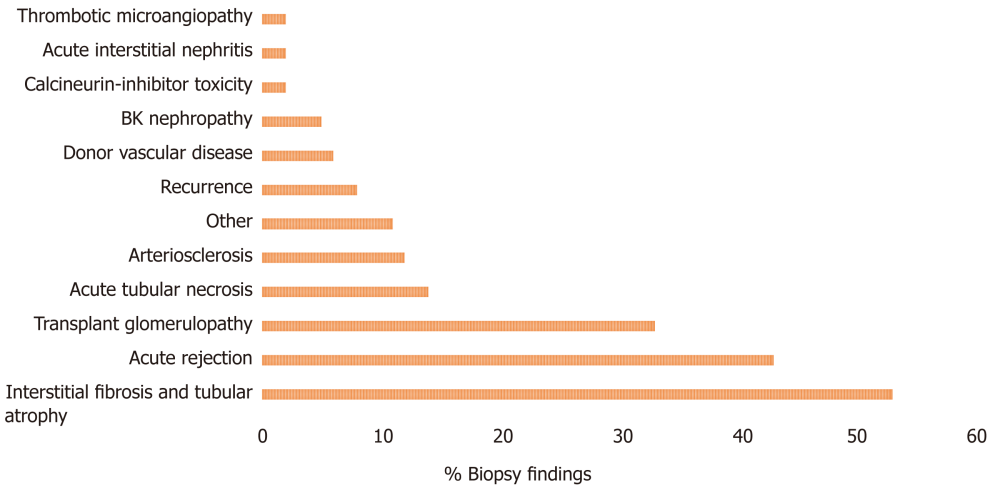

Figure 2 All histological findings on the biopsy. Interstitial fibrosis and tubular atrophy, acute rejection, and transplant glomerulopathy were the common histological findings in the failing graft.

DISCUSSION

In this study of the cause of graft failure among KTRs, we found that the primary cause of graft failure varies with time after transplantation. AR, mainly ABMR, was the most common cause of graft failure and accounted for 40% of graft failures, which peaked at 6 years post-transplant. After an AR, TG, one of the most specific histological findings of chronic ABMR[11], accounted for 17% of graft failure, which occurred mainly after 6-7 years post-transplant and was the most common cause of graft failure and even surpassed AR as a cause of graft failure. With careful adjustment of CNI dosing and with close monitoring of trough level, CNI toxicity was not a prevalent cause of graft failure in our cohort, which was considered one of the common cause of graft failure in the past.

There has been a dramatic improvement in the rate of AR. The half-life of a standard criteria deceased donor kidney in the United States has increased by almost 50%, from 10.6 years in 1989 to 15.5 years in 2005, and a similar pattern was seen with living donor transplantation[5]. This change was paralleled by a dramatic decline in graft failure within the first-year post-transplant period. Unfortunately, death-censored graft failure beyond the first year has remained unchanged since 1989[12]. During this time, our understanding of rejection and management have evolved, and graft failure due to hyperacute rejection is very rare. With newer protocols, ACR rates have decreased to less than 10% in the first year[5]. In the current era, our focus is on the prevention and treatment of ABMR. Certain newer therapeutics are considered for ABMR treatment based on their mechanism of action, such as anti-CD20 antibodies (*e.g.*, ofatumumab and ocrelizumab), anti-CD22 antibody (epratuzumab), agents targeting B cell activation (*e.g.*, atacicept and belimumab), and Anti-C5 antibody (eculizumab)[13-15], and others potentially in the investigational pipeline. Most of the work is being conducted in the fields of prevention and treatment of AR, and in time we may be able to effectively manage AR including acute ABMR. However, chronic changes and the lesser understood mechanisms of TG and IFTA may hinder our aim of prolonged graft survival.

TG has evolved as one of the histological features of chronic ABMR[16]. Overt TG is characterized histologically by glomerular basement membrane duplication in ≥ 1 of the capillary loops, mesangial expansion with or without mesangial hypercellularity, and mesangial cell interposition; glomerulitis can accompany these lesions[17]. The overall incidence of TG increases with time after transplant, occurring in approximately 20% by 5 years post-transplant[18,19]. TG is rarely diagnosed clinically within the first year of transplant, as TG lags behind the initial histologic stages of the disease[18]. In one study, subclinical TG (with stable renal function) was diagnosed in a protocol biopsy at a rate of 2.8% in the first year, which increased to 11.5% by 5 years post-transplant[18]. TG with significant proteinuria (> 2.5 g/day) is associated with worse graft survival outcomes compared with those with less proteinuria[20]. In the biopsy, TG is usually accompanied with the features of chronic damage to the allograft parenchyma mainly as fibrous intimal thickening of arteries, arteriolar hyalinosis and segmental and/or global glomerulosclerosis, IFTA and sometimes failure of peritubular capillaries[16]. Among patients with TG and active ABMR,

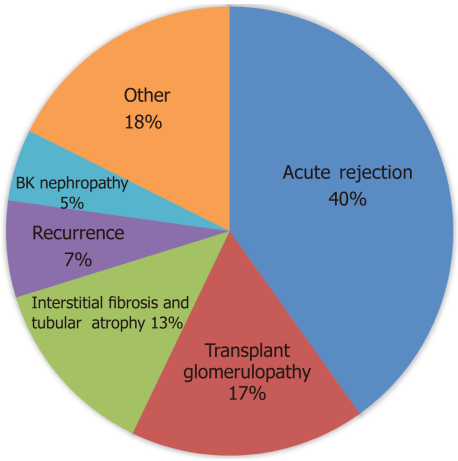

Figure 3 Overall causes of graft failure. Acute rejection is the most common cause of graft failure based on the primary biopsy diagnosis.

outcomes are even worse; in one large observational study, 76% of the recipients lost their graft with a median survival of 1.9 years after the diagnosis of chronic active ABMR[21]. Overall, TG is associated with poor long-term graft survival, as grafts with TG fail sooner than those without[22]. Much effort is being made to investigate therapeutic options for the treatment of TG. Cooper *et al*., studied the effects of high-dose IVIG in chronic ABMR and did not find any favorable outcomes. Nine of 20 treated patients in their study had a follow-up biopsy and only 4 had no histological progression[23]. Similarly, in a recent randomized double-blinded clinical trial, the addition of IVIG and rituximab was not useful in patients with TG[24].

IFTA is a final common pathway involving a number of independent and overlapping cellular and molecular pathways[25]. In a recent study, prior ACR was associated with inflammation within IFTA and presence of inflammation within IFTA was associated with accelerated IFTA, arterial hyperplasia and chronic glomerulopathy along with reduced renal function compared to those without inflammation[26]. There is no reliable way to differentiate the cause of IFTA based on the morphology alone, or immunohistochemistry and molecular techniques[27]. Tubular atrophy and interstitial fibrosis progress in parallel[28]. In one surveillance biopsy among 321 KTRs, interstitial fibrosis was present in 71% of the graft at two years[28]. To date, there is no consensus about the mechanism or treatment for IFTA but chronic immune rejection and inflammation is considered one of the mechanisms[29]. Also, immune cell-derived and locally active complement has been associated with the progression of chronic fibrosis[30]. These suggest that although not as strong association as with TG, IFTA could be related to an immune-derived mechanism leading to graft loss.

Calcineurin inhibitor toxicity, thrombotic microangiopathy, and other causes of graft loss each contributed to 5% or less to graft failure. Our observations have the limitations inherent in this type of study. As a single-center study, it may not be possible to generalize our results to other centers. We looked for the specific causes of graft failure based on the primary biopsy diagnosis, but the specific management based on the biopsy findings was beyond the scope of this study. Similarly, around 50% of our patient population were excluded due to no biopsy within one year prior to the graft failure and it was not possible to determine the histopathological characteristics of those patients. We also excluded the small number of patients with primary graft dysfunction to avoid any surgical and technical issues for graft failure.

In summary, AR is still the most common cause of early graft failure in the current era of immunosuppression. Most early graft failures within the first six years of transplant are related to AR and are in theory preventable. Similarly, more effective diagnostic, monitoring, and therapeutic strategies for TG and IFTA are needed to improve long-term graft survival.

Table 2 Histopathological characteristics of graft failure based on the cause of end stage renal disease, *n* (%)

	Glomerulonephritis (*n* = 99)	Diabetes (*n* = 71)	Hypertension (*n* = 35)
Acute rejection	49 (49)	21 (30)	19 (54)
Transplant glomerulopathy	14 (14)	14 (20)	4 (11)
Interstitial fibrosis and tubular atrophy	11 (11)	12 (17)	5 (14)
BK nephropathy	3 (3)	7 (10)	2 (6)
Acute tubular necrosis	1 (1)	5 (7)	3 (9)
Recurrence	6 (6)	6 (8)	1 (3)
Other	15 (15)	6 (8)	3 (9)

Table 3 Histopathological characteristics of graft failure based on the induction immunosuppressive agent, *n* (%)

	Depleting (127)	Non-depleting (*n* = 202)	*P* value
Acute rejection	46 (36)	86 (43)	0.25
Transplant glomerulopathy	31 (24)	96 (48)	0.003
Interstitial fibrosis and tubular atrophy	13 (10)	30 (15)	0.23
BK nephropathy	7 (6)	10 (5)	0.82
Acute tubular necrosis	6 (5)	10 (5)	0.92
Recurrence	6 (5)	8 (4)	0.74
Other	18 (14)	34 (17)	0.52

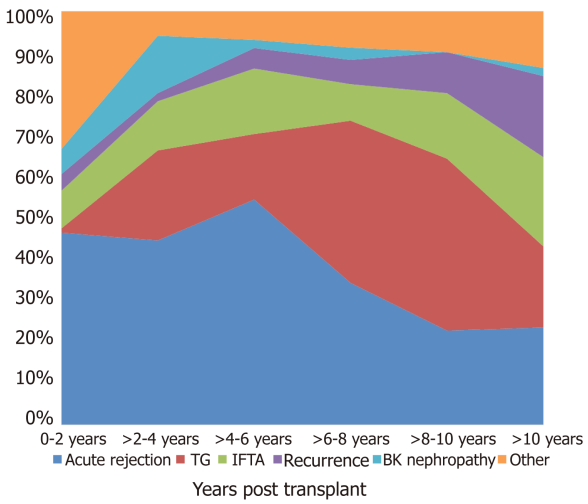

Figure 4 Causes of graft failure since time of transplant. IFTA: Interstitial fibrosis and tubular atrophy.

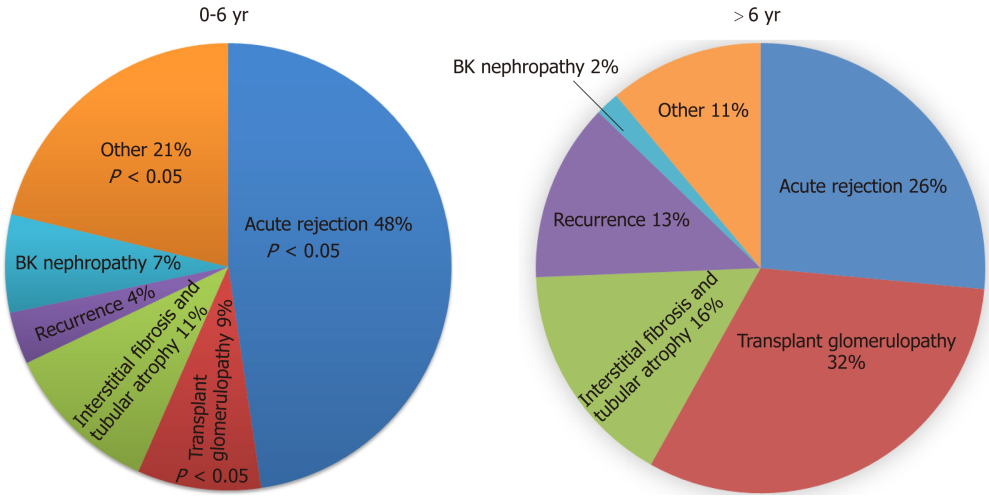

Figure 5 Transplant glomerulopathy is the predominant cause of graft failure after the 6th year. $P < 0.05$ compared to > 6 yr between acute rejection, transplant glomerulopathy and other.

ARTICLE HIGHLIGHTS

Research background

Although, there have been significant improvements in early graft survival due to advances in immunosuppression and the overall medical care of transplant recipients. However, long-term graft survival has only had modest improvement. The causes of "true" late kidney allograft failure remain unclear.

Research motivation

In this study, we explored the causes of graft failure based on various histopathological findings after transplant in the current era, which may allow providers to determine interventions to prevent poor outcomes.

Research objectives

The main objectives, of this study, was to identify the common causes of death censored graft failure among kidney transplant recipients. Knowing the causes may help provider to intervene on time and prevent for the graft loss.

Research methods

This was a single-center, retrospective study among kidney transplant recipients who were transplanted at the University of Wisconsin, and who had graft failure between January 1, 2006 and December 31, 2016 and transplanted between January 1, 1994 to December 31, 2016. Patients were included if they underwent a kidney biopsy within one year prior to the graft failure. We divided histopathological causes of graft failure based on the post-transplant interval divided into 2 years interval, based on the causes of ESRD and also the types of induction immunosuppressive medication. In cases where a patient had multiple biopsy diagnoses, all diagnoses were also reported separately, although the primary diagnosis (first diagnosis) was used for the cause of graft failure.

Research results

A total of 329 kidney transplant recipients fulfilled our selection criteria and were included in the study. The three most common biopsy findings were interstitial fibrosis and tubular atrophy (IFTA, 53%), acute rejection (AR, 43%) and transplant glomerulopathy (TG, 33%). Similarly, the three most common causes of graft failure based on the primary diagnosis were AR (40%), TG (17%), and IFTA (13%). Most grafts failed within two years of post-transplant (36%). Subsequently, approximately 10%-15% of grafts failed every two years: > 2-4 years (16%), > 4-6 years (13%), > 6-8 years (11%), > 8-10 years (9%) and > 10 years (16%). AR was the most common cause of graft failure in the first six years (48%), whereas TG was the most prevalent cause of graft failure after 6 years (32%) of transplant. Most early graft failures within the first six years of transplant are related to AR and are in theory preventable. Similarly, more effective diagnostic, monitoring, and therapeutic strategies for TG and IFTA are needed to improve long-term graft survival.

Research conclusions

In this study of the cause of graft failure among kidney transplant recipients, we found that the primary cause of graft failure varies with time after transplantation. AR, mainly antibody-mediated rejection (ABMR), was the most common cause of graft failure and accounted for 40% of graft failures, which peaked at 6 years post-transplant. After an AR, TG, one of the most specific histological findings of chronic ABMR, accounted for 17% of graft failure, which

occurred mainly after 6-7 years post-transplant and was the most common cause of graft failure and even surpassed AR as a cause of graft failure. Interestingly, calcineurin inhibitor toxicity was not a common cause of graft failure.

Research perspectives

Further studies in this field and specifically effective treatment of AR is needed to prolong the graft survival. Most of the work is being conducted in the fields of prevention and treatment of AR, and in time we may be able to effectively manage AR including acute ABMR. However, chronic changes and the lesser understood mechanisms of TG and IFTA may hinder our aim of prolonged graft survival and study should focus on the field of prevention or treatment of TG and IFTA.

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ORIGINAL ARTICLE

Retrospective Study

Efficacy and safety of non-vitamin K antagonist oral anticoagulants post-kidney transplantation

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Abstract

BACKGROUND

Novel oral anticoagulants (NOACs) were developed as alternatives to vitamin K antagonists, primarily warfarin, as they do not require routine monitoring and have limited drug-drug and drug-food interactions. However, the efficacy and safety of these agents in kidney transplantation are not well studied.

AIM

To assess the profile and safety of NOACs for patients who had kidney transplantation, and to provide recommendations and guidelines on therapeutic strategies in these patients.

METHODS

This was a retrospective study carried out among adult patients who were actively on the following NOACs (apixaban, rivaroxaban or dabigatran) in our renal transplantation program from December 2015 to December 2016. The patients were identified primarily through electronic medical record system (patient data linkage). Data on the clinical and laboratory profile of the patients were retrieved and analyzed with SPSS 22.0.

RESULTS

Complete data on 42 renal transplant patients were retrieved: 59.5% males, 90.5% were whites and 66.7% were older than 60 years old. The mean duration since renal transplantation of the patients was 8.8 ± 7.4 years. The most common risk

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factors for the development of end-stage renal disease in the subjects were hypertension (19.0%), polycystic kidney disease (19.0%), followed by diabetic nephropathy (16.7%) and chronic glomerulonephritis (16.7%). The main indications for NOACs use in the cohort were atrial fibrillation in 25 patients (59.5%) and venous thromboembolism in 10 patients (23.8%). Overall, 29 patients (69%) were treated with apixaban, 10 patients (23.8%) with rivaroxaban and 3 patients (7.14%) with dabigatran. No (0%) thromboembolic events were observed during the one-year period, but 3 (7.1%) bleeding events occurred in the cohort consisting of 1 patient treated with rivaroxaban 15 mg daily and 2 patients who received apixaban 2.5 mg twice daily. There were no significant changes in serum tacrolimus level three days after the initiation of NOACs among patients treated with tacrolimus (pre- and post-NOACs tacrolimus levels were 7.2516 and 7.8867 ng/mL, $P = 0.55$, respectively). Also, after one-year of treatment with NOACs there were no significant changes in the pre- and post-NOACs serum creatinine level ($P = 0.772$) and estimated glomerular filtration rates ($P = 0.232$).

CONCLUSION
No thromboembolic events or significant changes in renal profile were observed in our cohort of kidney transplant recipients who were treated with NOACs for at least a year. However, a few bleeding events were observed. This calls for further well-planned randomized controlled trials to assess the efficacy and safety of NOACs among renal transplant recipients.

Key words: Novel oral anticoagulants; Adult patients; Kidney transplantation; Renal outcomes; Efficacy

Core tip: No consensus is available in the literature about whether novel oral anticoagulants are effective and safe for renal transplant recipients. This is one of the first attempts to investigate the profile, safety and effectiveness of novel oral anticoagulants for adult renal transplant recipients. We investigated the role of novel oral anticoagulants in terms of its effect on thromboembolism, bleeding, creatinine clearance and immunosuppressive agents.

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INTRODUCTION

Non-Vitamin K antagonists also known as novel oral anticoagulants (NOACs) were developed as alternatives to vitamin K antagonists, primarily warfarin, as they do not require routine monitoring and have limited drug-drug and drug-food interactions[1]. NOACs are gaining popularity over the past few years as stroke-preventing agents for people with atrial fibrillation (AF)[1]. NOACs have also been recommended for the treatment of systemic embolic events in patients with nonvalvular AF and for the treatment of venous thromboembolism (VTE)[1-3]. They are recommended by the Canadian Cardiovascular Society guidelines for the management of AF with a class I recommendation[4]. Four NOACs, (dabigatran, rivaroxaban, apixaban, and edoxaban) have received approval from the United States Food and Drug Administration for the prevention of AF.

Kidney transplantation is considered the treatment of choice for patients with end-stage renal disease (ESRD) and has been shown to improve quality of life and survival rate for most patients compared to those maintained on dialysis[5,6]. AF occurs in over 7% of kidney transplant recipients in the first 3years after transplantation and is associated with reduced graft and patient survival[7]. NOACs represent a valuable anticoagulation therapy for kidney transplant recipients, which are at higher risk of

bleeding and thrombotic complications. However, NOACs use in renal transplant patients is not yet recommended as they are excreted via kidney and there are concerns it may interact with immunosuppressive therapy[5,7]. Indeed, as substrates of CYP3A4, apixaban and rivaroxaban, and p-glycoprotein, dabigatran; NOACs were suggested to interact with calcineurin inhibitors (CNIs) in a small retrospective study[8]. In heart and lung transplant recipients, a recent study showed that NOACs were effective and safe but associated with high rate of drug interactions that require dose reduction (by 45%)[9].

Given the fact that NOACs don't require frequent monitoring and due to their low interactions and lower risk of spontaneous bleeding, these agents carry a great advantage over warfarin[1]. However, the efficacy and safety of these agents in kidney transplantation are not well studied yet. In this study, we aimed to assess the safety of NOACs administration in patients after kidney transplantation, and to provide recommendations and guidelines on therapeutic strategies in these patients.

MATERIALS AND METHODS

This was a retrospective study carried out among adult patients who were actively on the following NOACs (apixaban, rivaroxaban or dabigatran) in our renal transplantation program from December 2015 to December 2016. The patients were identified primarily through the electronic medical record system (patient data linkage). We also included renal transplant recipients whose anticoagulation therapy with NOACs were stopped or changed but had at least one-year record of use of NOACs corresponding with our study period (*i.e.*, up to one year of use be December 1, 2016).

Only records of adult patients (age ≥ 18 years) were included. Data of pediatric renal transplant recipients, adult patients with medication adherence issues, and those who stopped NOACs >12 mo prior to the study, were excluded from the analysis. The electronic records of the patients were retrieved from the electronic medical record system (Patient link). The data of patients with incomplete information were available in the electronic medical record system were extracted from the patients' paper charts. Data on the clinical and laboratory profile of the patients were extracted.

Statistical analysis

The study was approved by Hamilton Integrated Research Ethics Board (HiREB). Also, because this was a retrospective study of anonymized/deidentified electronic records, HiREB waived request for informed consent from patients. Data were analyzed with SPSS 22.0 (IBM Corp., NY, United States). Continuous variables were expressed as means ± standard deviations and categorical variables were expressed as percentages. Chi-square tests were used for categorical variables and unpaired *t*-tests and one-way analyses of variance were used to compare continuous variables. *P* values < 0.05 were considered significant. The statistical methods of this study were reviewed by Dr. Mamta Gupta PhD (Public Health and Epidemiology/MPH Epidemiology and Biostatistics) from the Department of Epidemiology and Biostatistics, Alchemist Research and Data Analysis, Chandigarh, 160 036, India.

RESULTS

Our cohort included a total of 47 patients; only 42 patients were retained for further analysis after excluding 5 patients due to incomplete data. The clinical characteristics of patients are presented in Table 1. Most patients were males 25 (59.5%) and the vast majority 28 (66.7%) were older than 60 years old with 11 (26.2%) being ≥ 75 years old. The mean age in our cohort was 64.7 ± 13.88 years. The mean duration since renal transplantation of the patients was 8.8 ± 7.4 years (range 1 to 30 years). The average estimated glomerular filtration rate (eGFR) was 62.90 ± 18.98 mL/min/1.73 m^2. No significant difference in eGFR among age groups was noticed. A total of 38 patients were white (90.5%); only 2 were Asian, 1 Indian and 1 Hispanic. The Most common causes of ESRD in our cohort were hypertension and polycystic kidney disease, occurring in 8 patients (19.0%) each, followed by 7 patients with diabetic nephropathy and chronic glomerulonephritis (16.7%) (Table 2).

A total 29 patients (69%) were treated with apixaban, 10 patients (23.8%) with rivaroxaban and 3 patients (7.14%) with dabigatran (Table 2). Among those that were on apixaban, 58.6% were on low dose of 2.5 mg bid and 41.3% were on full dose of 5 mg bid. Similarly, of the 10 patients on rivaroxaban, 5 were on a full daily dose of 20 mg and 5 were on reduced daily dose of 15 mg. In our cohort, 25 patients (59.5%)

Table 1 Demographic characteristics of the patients

Age	No. patients	Age (yr, mean ± SD)	No. males	Weight	*n*	Estimated glomerular filtration rate
≤ 30	1	30	0	52	0	54
31-45	5	40.4 ± 5.86	2	96.20 ± 31.06	2	56.00 ± 18.67
46-60	8	56.4 ± 2.51	6	98.88 ± 29.79	3	65.13 ± 21.94
> 60	28	72.0 ± 6.71	17	78.25 ± 14.77	14	63.82 ± 18.88
Total	42	64.7 ± 13.88	25	83.69 ± 22.32	19	62.90 ± 18.98

Estimated glomerular filtration rate in (mL/min/1.73 m^2).

were on NOACs due to AF, 10 patients (23.8%) due to VTE and 5 patients (11.9%) due to both AF and VTE. Most patients were on tacrolimus-based anti-rejection (immunosuppressive) therapy (31; 76.8%) and 5 patients (11.9%) were on a cyclosporine-based regimen, and only 4 patients (9.6%) were on sirolimus-based regimen. In addition, all the 42 patients (100%) received oral prednisolone and mycophenolate mofetil. Table 3 shows the profile of the immunosuppressive agents received according the type of NOAC agent. NOACs were used without a concomitant antiplatelets therapy in 37 of the patients (88.1%).

Overall, we observed 3 bleeding events (7.1%) in our cohort consisting of 1 patient treated with rivaroxaban 15 mg daily and 2 patients who received apixaban 2.5 mg twice daily (Table 4). One of these was a major bleeding event which occurred while rivaroxaban was on hold for over a month in preparation for a cataract surgery. The patient had a background of severe retinopathy and had intraocular bleeding one day after the surgery. This bleeding event was assumed to be unrelated to the medication, and rivaroxaban was resumed a few months later. This patient didn't experience any further bleeding events after rivaroxaban resumption. The other two bleeding events were bleeding per-rectum events that occurred in two ladies on low-dose apixaban. There were no significant reduction in the patients creatinine, eGFR or CNI levels at the time of the events. The bleeding events in both cases were minor, didn't cause hemodynamic instability, and didn't require surgical intervention or complete cessation of NOACs.

On the other hand, no thromboembolic events (0%) were observed. In addition, no significant change in serum tacrolimus level was observed three days after the initiation of NOACs among patients treated with tacrolimus (pre- and post-NOACs serum tacrolimus level was 7.25 and 7.89 ng/mL, $P = 0.55$). Similarly, after one year of treatment with NOACs there was no significant change in the pre- and post-NOACs serum creatinine level with mean levels of 107.6 μmol/L and 113.11 μmol/L ($P = 0.772$) respectively, (median 107.5 *vs* 108.5 μmol/L, respectively). This is summarized in Figure 1. Besides, as shown in Figure 2, pre- and post-NOACs eGFR levels after one-year of treatment with NOACs did not significantly change with respective mean levels of 72.2 mL/min/1.73 m^2 and 65.9 mL/min/1.73 m^2 ($P = 0.232$; median: 68.2 *vs* 60.4 mL/min/1.73 m^2, respectively).

DISCUSSION

Dabigatran was the first NOAC agent released into the European market for VTE prophylaxis post joint replacement surgeries in 2008[1]. It was the first NOAC agent to get Food and Drug Administration approval for AF in 2010, and VTE in 2014. International recommendations suggested the need to change NOACs name from novel oral anticoagulation drugs to non-vitamin K antagonist agents keeping the same acronym; NOACs[10].

To our knowledge, this is the first study that addresses the efficacy and safety of NOACs in kidney transplantation recipients. Our results show that NOACs treatment has no effect on kidney function. Indeed, none of the NOACs used in our study induced changes in creatinine or eGFR levels after treatment. A previous study on lungs and heart transplantation suggested that NOACs can interact with CNIs[9]. Moreover, Wannhoff *et al*[11] suggested that cyclosporine has a higher rate of drug interaction with rivaroxaban in another liver transplantation study. On the other hand, Vanhove *et al*[12] reported similar, but clinically insignificant (< 20% change), interaction that didn't warrant CNI dose adjustments in transplant recipients.

In our study, we didn't report any thromboembolic event in any of the patients after CNI initiation. This might suggest NOACs are as effective in kidney trans-

Table 2 Clinical characteristics of the patient groups, *n* (%)

Variable	Age group (yr)		Total
	< 75	≥ 75	
Primary cause of ESRD			
Diabetic nephropathy	6 (19.4)	1 (9.1)	7 (16.7)
Hypertension	6 (19.4)	2 (18.2)	8 (19.0)
Glomerulonephritis	4 (12.9)	3 (27.3)	7 (16.7)
Polycystic kidney disease	6 (19.4)	2 (18.2)	8 (19.0)
Chronic Interstitial nephritis	3 (9.7)	1 (9.1)	4 (9.5)
Reflux/Congenital	3 (9.7)	2 (18.2)	3 (7.1)
Other	3 (9.7)	2 (18.2)	5 (11.9)
NOACs			
Dabigatran 150 mg bid	1 (3.2)	1 (3.2)	2 (4.8)
Dabigatran-Low Dose	1 (3.2)	0 (0.0)	1 (2.4)
Apixaban 5 mg bid	11 (35.5)	1 (9.1)	12 (28.6)
Apixaban-Low Dose	10 (32.3)	7 (63.6)	17 (40.5)
Rivaroxaban 20 mg/d	5 (16.1)	0 (0.0)	5 (11.9)
Rivaroxaban Low Dose	3 (9.7)	2 (18.2)	5 (11.9)
Cause of NOAC initiation			
VTE	8 (25.8)	2 (18.2)	10 (23.8)
AF	17 (54.8)	8 (72.7)	25 (59.5)
Other	2 (6.5)	0 (0)	2 (4.8)
VTE and AF	4 (12.9)	1 (9.1)	5 (11.9)
Calcineurin inhibitors			
Advagraf	22 (71.0)	5 (45.5)	27 (64.3)
Prograf	3 (9.7)	1 (9.1)	4 (9.5)
Cyclosporin	1 (3.2)	4 (36.4)	5 (11.9)
Sirolimus	3 (9.7)	1 (9.1)	4 (9.5)
None	2 (4.8)	0 (0)	2 (4.8)
Clopidogrel			
Yes	4 (12.9)	1 (9.1)	5 (11.9)
No	27 (87.1)	10 (90.9)	37 (88.1)

NOACs: Novel oral anticoagulants; VTE: Venous thromboembolism; AF: Atrial fibrillation; ESRD: End stage renal disease.

plantation population as the general population. Also, we had a few bleeding events with low doses (2.5 mg twice daily) of apixaban and a moderate dose (15 mg daily) of rivaroxaban, which may suggest a good safety profile. However, there is a need to further assess the mechanisms of bleeding in patients exposed to NOACs. Although our study indicates that NOACs may be safe and effective for the prevention and treatment of thromboembolic events in renal transplant recipients, there is a need to highlight some of its important advantages and disadvantages compared to other vitamin K antagonists. Its major advantages include absence of food interactions, few strong drug interactions, predictable pharmacokinetic and pharmacodynamic properties, a rapid onset and offset of action, a short half-life, and the absence of the need for laboratory monitoring[13].

However, pharmacokinetic and pharmacodynamic studies show that NOACs elimination is dependent on renal clearance to varying extents; but compared with vitamin K antagonists, the efficacy and safety of the NOACs is preserved in patients with moderate renal impairment[14,15]. There is a need to administer NOACs with caution in individuals with severe kidney or hepatic damage particularly the elderly. This is because up to 25%, 33% and 80% of apixaban, rivaroxaban and dabigatran, respectively are eliminated through the kidneys as an active drug[13-15]. In severe renal or hepatic damage, the elimination of the drug may be affected requiring adjustments in the dosing of the NOAC agent.

Our analysis only included renal transplant recipients with an eGFR of > 54 mL/min/1.73 m^2. Therefore, dosage adaptation of the NOACs should ideally not be

Table 3 Profile of the cases that developed bleeding

	Case 1	Case 2	Case 3
Age	77	73	87
Gender	Male	Female	Female
NOACs on use	Rivaroxaban	Apixaban	Apixaban
NOACs dose	15mg daily	2.5mg bid	2.5mg bid
Type of bleeding	Major	Non-major	Non-major
Site of bleeding	Intra-ocular	Bleeding per rectum	Bleeding per rectum
Time to bleed	> 1 yr post starting	> 1 yr post starting	> 1 yr post starting
Base line Cr/eGFR	93/72.6	67/79.5	122/38.44
Cr/eGFR at bleeding	144/38.6	58/93.9	147/31.0
CNI in use	Cyclosporin	Tacrolimus	Cyclosporin
CNI level at bleeding time	C0: 91	5.8 (within target)	C0: 116
Antiplatelet used	None	None	None
note	Rivaroxaban was on hold at the time of bleeding. Bled post cataract surgery.		

NOACs: Novel oral anticoagulants; CR: Creatinine; eGFR: Estimated glomerular filtration rate; CNI: Calcineurin inhibitors.

necessary. However, considering the very limited or no prior experience in the use of NOACs in kidney transplant recipients (with/without renal impairment), doses of NOACs were administered to the patients in this study using the Health Canada dosing algorithm for each of the NOACs according to renal function and clinical status of the patients[14,16]. Thus, the effectiveness of NOACs observed in our data can only be interpreted in the context of kidney transplant recipients with sufficiently preserved renal function. Several clinical trials such as the EINSTEIN, ARISTOTLE, and RE-LY trials have previously demonstrated the safety and efficacy of these NOACs in individuals with varying levels of renal impairment[17-19].

In the present study, 3 of the subjects received dabigatran with tacrolimus-based CNIs. Previous studies have called for caution in the use of NOACs and immunosuppressive agents due to the potential for drug-drug interactions[8,20,21]. A study suggested that dabigatran should not be administered to patients receiving CNIs because CNIs are known substrates of both CYP 450 3A4 and P-gp, and can lead to increased exposure to dabigatran[8,20]. Because of the limited evidence of NOACs usage with CNIs in the setting of solid organ transplantation, this clinical recommendation was made based on an underpowered analysis of nine heart transplant recipients immunosuppressed with CNIs and treated with dabigatran for AF, VTE, or atrial thrombus[8]. In the study, patients who received tacrolimus with dabigatran were more likely to require a decrease in tacrolimus dose during therapy and numerically had more major bleeding events[8]. However, observations from the RE-LY trial indicate that concomitant use of dabigatran with P-gp inhibitors (like amiodarone or verapamil) increased dabigatran exposure but was not associated with significant differences in the event rate or bleeding[22,23]. A recent review indicates that in patients receiving dabigatran etexilate for the treatment and prevention of VTE, there is no need for dose adjustments and no contraindication to its co-administration with P-gp inhibitors so long as the patients have a creatinine clearance greater than 50 mL/min[24]. All the patients in our study had creatinine clearance greater than 50 mL/min and none of those who received dabigatran had a bleeding event. Recent expert opinion conclude that provided adequate attention is given to renal function, the co-administration of NOACs and CNIs in solid organ transplantation is safe and effective[24].

This study has some limitations. First, this was a retrospective observational study, therefore any reported association does not imply causation. Second, all the patients in this study had sufficiently preserved renal function (creatinine clearance > 50 mL/min), therefore we cannot report on the safety or efficacy of the NOACs in kidney transplant recipients with substantial renal impairment. Third, more than half of the patients received low doses of the NOAC agent. Therefore, our finding may not reflect the outcomes in renal transplant recipients treated with higher doses of NOAC agent.

In conclusion, our study suggests that NOACs may be safe and effective for the prevention and treatment of thromboembolic events in renal transplant recipients with limited complications. Further studies need to be conducted to assess the

Table 4 Profile of the immunosuppressive agents received according the type of Novel oral anticoagulants agent

NOAC	Calcineurin inhibitor used, *n* (%)					Total
	Advograf	Pyograf	Cycosporin	Sirolimus	None	
Dabigatran 150 mg bid	2 (7.4)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4.8)
Dabigatran-low dose	1 (3.7)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.4)
Apixaban 5 mg bid	8 (29.6)	1 (25.0)	0 (0)	2 (50.0)	1 (50.0)	12 (28.6)
Apixaban-low dose	10 (37.0)	2 (50.0)	3 (60.0)	2 (50.0)	0 (0)	17 (40.5)
Rivaroxaban 20 mg/d	4 (14.8)	1 (25.0)	0 (0)	0 (0)	0 (0)	5 (11.9)
Rivaroxaban low dose	2 (7.4)	0 (0)	2 (40.0)	0 (0)	1 (50.0)	5 (11.9)

All patients also received prednisolone and mycophenolate mofetil. NOACs: Novel oral anticoagulants.

effectiveness and safety profile of NOACs compared to other vitamin K antagonists (*e.g.*, warfarin) in kidney transplant population.

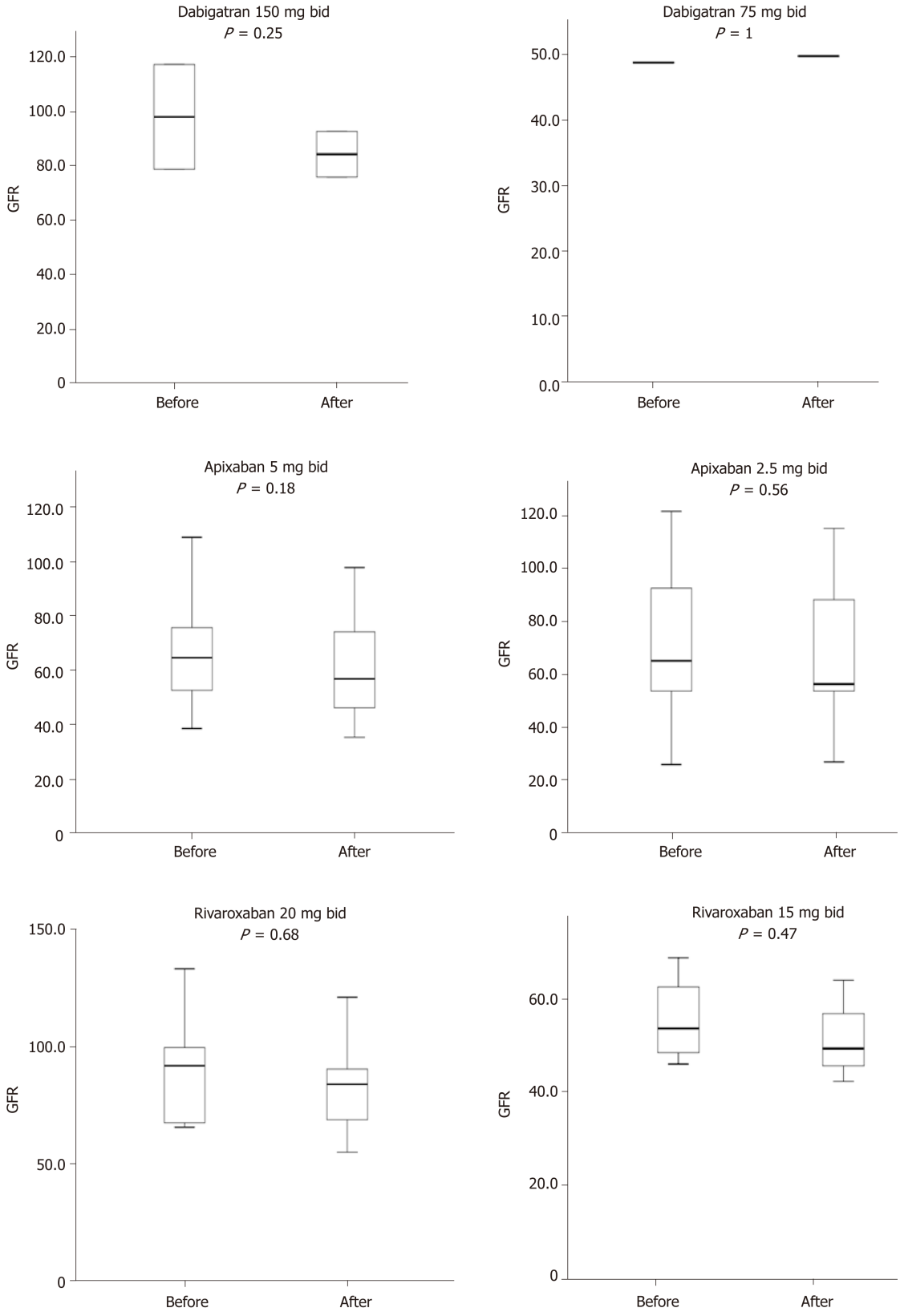

Figure 1 Creatinine levels before and after treatments with novel oral anticoagulants. Boxplots showing the distribution of creatinine levels (μM) before and after novel oral anticoagulants treatment. Points indicate individual patients, with colors representing age groups.

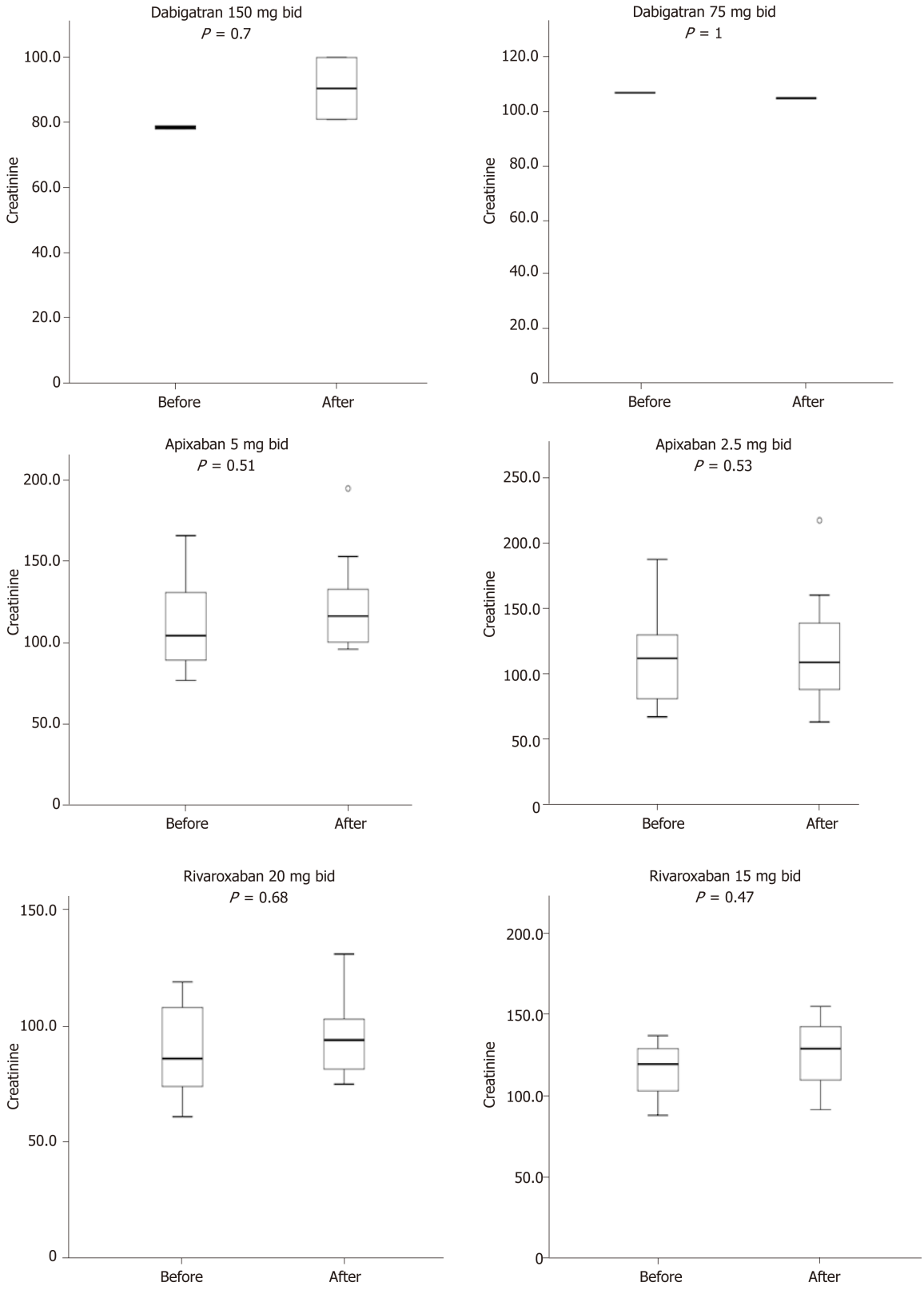

Figure 2 Estimated glomerular filtration rate before and after treatments with novel oral anticoagulants. Boxplots showing the distribution of estimated glomerular filtration rate levels (mL/min/1.73 m^2) before and after novel oral anticoagulants treatment. Points indicate individual patients, with colors representing age groups.

ARTICLE HIGHLIGHTS

Research background

Novel oral anticoagulants are increasingly being used in recent times for preventing stroke in individuals with atrial fibrillation and for the management of systemic embolic events and

venous thromboembolism. With the increased risk of atrial fibrillation and thrombotic events observed in kidney transplant recipients, whether novel oral anticoagulants have clinical significance in this group of patients remains unclear.

Research motivation

Novel oral anticoagulants are being used as an oral anticoagulation agent for the prevention of embolic events in individuals with atrial fibrillation and for the treatment of venous thromboembolism. They also have the advantage of not requiring frequent monitoring and having a lower adverse effects profile. There are concerns regarding the clinical use of novel oral anticoagulants in renal transplant recipients because of its renal excretion and the likelihood of its interaction with immunosuppressive agents. Although, novel oral anticoagulants have successfully been used for anticoagulation in heart-lung transplant recipients, its use for this role in kidney transplant recipients is unknown.

Research objectives

We performed this retrospective study to assess the efficacy and safety of novel oral anticoagulants administration in patients after kidney transplantation, and to provide recommendations and guidelines on therapeutic strategies in these patients.

Research methods

This was a retrospective study carried out among adult patients who were actively on the following novel oral anticoagulants (apixaban, rivaroxaban or dabigatran) in our renal transplantation program from December 2015 to December 2016. The outcomes of interest include the profile of the patients, thromboembolic and bleeding events, and kidney dysfunction.

Research results

The authors observed 3 (7.1%) bleeding events in the cohort. Also, no (0%) thromboembolic events were observed. In addition, no significant changes in pre- and post- novel oral anticoagulants tacrolimus level, creatinine level, and estimated glomerular filtration rates were observed.

Research conclusions

Novel oral anticoagulants appear to be as effective in the renal transplantation population as in the general population. Also, we had a few bleeding events and no changes in renal function after the initiation of novel oral anticoagulants which suggests a good safety profile.

Research perspectives

This study demonstrated that novel oral anticoagulants are safe and effective in renal transplant recipients. There is a need for further clinical studies to assess the mechanisms of bleeding in patients exposed to novel oral anticoagulants. Randomised controlled trials are needed to compare the effectiveness and safety of novel oral anticoagulants compared to other vitamin K antagonists (*e.g.*, warfarin) in kidney transplant population.

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