Review Article

Preventing Renal Transplant Failure

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Abstract

Introduction: Allograft failure due to immunological or non-immunological causes or a combination and patient death after transplantation are the 2 major causes of renal transplant loss. This paper reviews the various causes of allograft failure and explores strategies for its prevention. Results: Immune mechanisms of renal allograft failure are those mediated by acute and chronic rejection and are initiated by human leukocyte antigen (HLA) disparity between donor and recipient and increased recipient immune responsiveness that results in pre-sensitisation against HLA antigens. Better HLA matching between donor and recipient in both live-donor and cadaveric renal transplant recipients and the use of more potent immunosuppressants has reduced the incidence of acute rejection and resulted in improved overall graft survivals in recent years. However, as the use of more potent immunosuppression increases the risk of infections and malignancy, tailoring therapy by administering more potent immunosuppression to those at higher immunological risk may result in a better balance between the risks and benefits of immunosuppressive therapies. Ischaemia of the donor kidney, calcineurin inhibitor (CNI), mediated nephrotoxicity, reduced renal mass, hypertension, hyperlipidaemia and infections contribute to allograft failure through non-immunological mechanisms. Indeed, any cause of renal injury that results in nephron loss, either immunological or non-immunological, leads to reduced renal mass and initiates further renal damage due to hyperfiltration. Optimising these factors and minimising CNI nephrotoxicity are critical in reducing chronic allograft failure. Conclusions: Optimising each of these time-dependent and immunosuppressive drug-related factors would allow the maximisation of renal allograft function and survival.

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Introduction

Renal transplantation is the best form of renal replacement therapy for patients with end-stage renal failure (ESRF), in comparison to dialysis, as it is associated with higher patient survivals, lower hospitalisation rates and a superior quality of life. However, the ever-increasing numbers of new patients with ESRF and the limited but static supply of donor kidneys for transplant mandate that every renal transplant be optimised to achieve long-term patient and allograft survival. Patient death after transplantation and allograft failure are the 2 major causes of transplant loss. Although patient survival following a renal transplant is higher than that for ESRF patients on dialysis, renal transplant (RTx) recipients nevertheless remain at risk for death from cardiovascular disease due to their prior history of renal disease, hypertension, excess atherosclerotic vascular disease and other comorbidities such as diabetes, and at risk for death from infection because of the need for long-term immunosuppression. At the Singapore General Hospital, RTx recipients transplanted under cyclosporine (CsA)-based therapy between 1994 and 1999 had overall 1- and 5-year patient survivals of 99% and 97% for live-donor (LD) grafts and 96% and 92% for cadaveric (CAD) grafts and 1- and 5-year graft survivals of 98% and 92% for LD grafts and 87% and 79% for CAD grafts respectively.[1] Among those who died or sustained graft loss after LD or CAD transplant, 6% of LD and 27% of CAD RTx, respectively, had died with a functioning allograft; the remainder lost their allografts to immunological and non-immunological causes. Thus, allograft failure over time

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after renal transplantation is a significant problem and poses challenges in the management of RTx.

The major causes of allograft failure can be broadly classified into clearly immunological causes such as acute rejection (AREJ) and chronic rejection (CREJ) and clearly non-immunological causes such as surgical problems, renovascular thrombosis, nephron injury due to various causes including ischaemia-reperfusion and nephrotoxicity from calcineurin inhibitors (CNI). In addition, a significant proportion of allograft failures can be attributed to recurrence of original disease or chronic allograft nephropathy (CAN), which is likely mediated by multiple mechanisms including immunological, non-immunological, haemodynamic and other factors. This article reviews these various causes of allograft failures in both the early and late periods after renal transplantation and proposes strategies to optimise allograft survival.

Immunological Causes

Immune injury due to T-lymphocyte-mediated or alloantibody-mediated AREJ is likely the single most important event adversely affecting renal allograft survival. Though most episodes of AREJ are reversible with pulse steroid or anti-lymphocyte antibody therapy, some, particularly more severe and alloantibody-mediated episodes, result rapidly in graft loss, while a significant proportion progress to CREJ or CAN over time post-transplant.[2] Indeed, a single episode of AREJ in the first year has been correlated with an approximately 50% reduction in renal allograft half-life (T1/2, an estimated time period for 50% of all kidney grafts surviving the first year to be lost).[3] Furthermore, the severity of the AREJ episode as well as the timing of the AREJ episode have implications for graft survival. Sijpkens et al[4] showed that 10-year graft survivals censored for causes of graft loss other than CREJ were 94%, 86% and 45% for patients without AREJ, with early AREJ (AREJ within 3 months) and with late AREJ, respectively. Not surprisingly, therefore, immunological factors such as human leukocyte antigen (HLA) mismatching and pre-sensitisation contribute to higher risks for graft loss from both AREJ and CREJ. The impact of these immunological factors on graft survival is particularly evident from large registry data.

HLA Mismatch

From the United Network of Organ Sharing (UNOS), the 17% statistically significant difference in 10-year graft survival between LD and CAD RTx (68% versus 51%, respectively) has been largely attributed to the better tissue matching in the former.[5] Indeed, HLA matching has had a significant impact on graft survivals since the azathioprine-steroid era of immunosuppression and this impact has persisted despite tremendous improvements in immuno-suppression over the last 3 decades. For RTx performed between 1995 and 2001, matching for antigens at the HLA-A,-B, and -DR loci resulted in a 16% higher projected 10-year graft survival rate when compared with RTx mismatched for 5 to 6 HLA antigens (P <0.001). The 3-year graft survival rates for zero HLA-B,-DR-mismatched or zero HLA-DR-mismatched RTx was 83%, significantly higher than the 80% and 77% 3-year graft survivals, respectively, for those with 1 or 2 DR antigens mismatched (P <0.001). Applying multivariate logistic regression analysis, Sijpkens et al[4] demonstrated that while delayed graft function (DGF) and HLA-DR mismatch were independent risk factors for early AREJ [odds ratio (OR) = 2.37 and 2.28 per antigen mismatch, respectively), HLA A and B mismatch was one of the risk factors for late AREJ (OR = 1.35 per mismatch of cross-reactive groups).

Pre-sensitisation

RTx recipients with lymphocytotoxic antibodies directed against HLA antigens (i.e., pre-sensitised) have also been demonstrated to have lower graft survivals than those without such antibodies from both single-centre and large multi-centre studies.[1,6] Though the most common causes of pre-sensitisation are rejection of a previous transplant, transfusions and pregnancies, up to 13% of non-transfused males and 20% of nulliparous females without prior transfusions have also been found to have such antibodies.[6] However, optimising tissue matching has been suggested to largely overcome the negative impact of pre-sensitisation as CAD re-transplants with zero HLA-DR mismatch had a 10% higher 3-year graft survival than those mismatched for 2 HLA-DR antigens.

Delayed Graft Function (DGF)

As defined by the requirement for dialysis in the first week post-transplant, DGF occurs in 20% to 30% of CAD RTx. From both single-centre and multi-centre studies, DGF has been demonstrated to have a significant negative impact on renal allograft survival. Though many non-immunological factors such as donor age and donor cause of death due to cerebrovascular accident (in contrast to donor death due to trauma) are associated with a higher risk for DGF, injury to the donor kidney by any means may trigger immunological mechanisms of allograft injury (Fig. 1). Thus ischaemia/reperfusion injury of an allograft, as that occurring during the harvest and transplantation procedures, may initiate a cascade of molecular events, including the activation of endothelial adhesion molecules and cytokine release, ultimately leading to leukocyte adherence and lymphocyte activation.[7] Immunological risk factors in the recipient such as pre-sensitisation or prior transplantation independently increase the risk for DGF as well as AREJ.

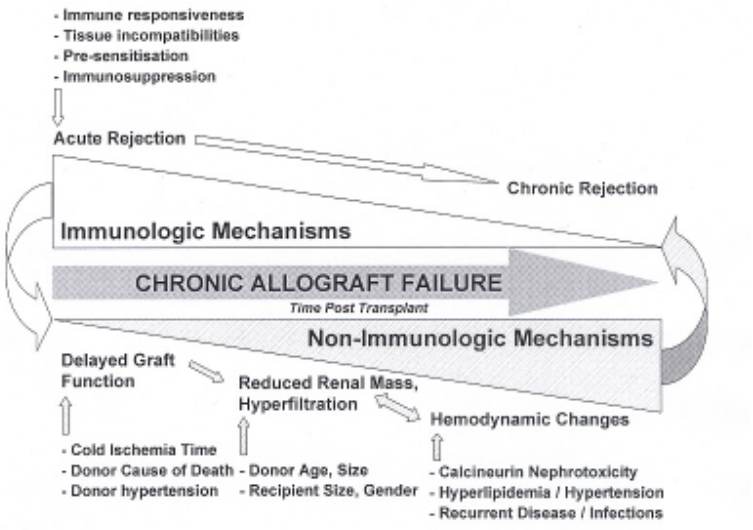

Fig. 1. Progression of chronic allograft failure. The time dependent nature of factors contributing to transplant failure as well as their inter-relationships are presented. With time post transplant, there is a decrease in immunological risk factors but an increase in non-immunological risk factors that contribute to chronic allograft failure. Immunological mechanisms may also trigger non-immunological mechanisms of injury during the course of transplantation and vice versa.

Strategies to Reduce Immunological Graft Loss

As suggested from the data presented above, LD renal transplantation should be the first option offered to ESRF patients as HLA matching and the quality of the donor kidney is better in LD than in CAD renal transplant; moreover, when the option is available, choosing the best HLA-matched kidney for either LD or CAD RTx will offer the best option for long-term allograft survival.

A second strategy to optimise outcomes post-transplantation is to rationalise the choice of immuno-suppressive therapy. Corticosteroids and azathioprine (AZA) have been used in clinical transplantation since the 1950s. Since the 1980s, new immunosuppressive agents, including CNI, which inhibit antigen signal transduction, inosine monophosphate dehydrogenase (IMPDH) inhibitors, which inhibit lymphocyte proliferation, target of rapamycin (TOR) inhibitors that prevent cell cycling, and monoclonal antibodies that block various lymphocyte receptors have been approved for use. Thus, given the wide array of immunosuppressants currently available for use in clinical transplantation, more potent agents can mitigate immunological risk factors.

Calcineurin Inhibitors

Indeed, since the clinical introduction of the first CNI, CsA, in the 1980s, both short- and long-term survivals have improved due to reduction in AREJ.[8] In 1997, tacrolimus (TAC), a second CNI, was introduced into clinical transplantation. Though some comparative clinical trials of TAC versus the microemulsion formula of CsA, Neoral, have demonstrated significantly reduced incidence of AREJ in RTx treated with TAC,[9] to date, long-term registry data have not shown a survival advantage for LD RTx treated with TAC-based therapies. Nevertheless, 5-year graft survivals among African-Americans, a population considered at high risk for AREJ, were significantly higher among those receiving TAC-based therapies following CAD RTx versus those receiving CsA-based therapies.[10]

Mycophenolate

Clinical trials in RTx recipients receiving a combination of the IMPDH inhibitor, mycophenolate mofetil, MMF, with CsA and steroids, in comparison with those on AZA, CsA and steroids, demonstrated a 2-fold reduction in the incidence of AREJ in the MMF-treated group (15.9% versus 35.5% in MMF versus AZA-treated respectively).[11] Though the 3-year results of these studies revealed equivalent graft survivals on comparison of those receiving either MMF or AZA, UNOS registry data suggest a survival advantage for RTx maintained on MMF-based therapies.[10,12,13]

Other Immunosuppressive Agents

Polyclonal antibodies against lymphocytes have been used to abrogate allo-immune responses in clinical renal transplantation since the 1960s. Anti-thymocyte globulins have been shown to reduce AREJ, improve graft survival and renal function in pre-sensitised RTx.[14] More recently, monoclonal antibodies directed against lymphocyte receptors have become available. In clinical trials, both basiliximab, a chimeric, monoclonal, anti-interleukin2 receptor antibody (IL2rAb), and daclizumab, a humanised IL2rAb monoclonal antibody, were demonstrated to reduce the incidence of AREJ among CAD RTx.[15,16] Long-term registry data are awaited to determine if the reduced incidence of AREJ following IL2rAb translates to improved long-term outcomes in renal transplantation.

In clinical trials of sirolimus (SIR), a TOR inhibitor,

together with CsA and steroids, reduced the incidence of AREJ (16.9% for 2 mg SIR versus 29.8% for AZA, $P = 0.002$).[17] Though to date there is no evidence of improved graft survival with this regimen, the non-nephrotoxic properties of SIR suggest a potential benefit of this agent in maintenance therapy (*vide infra*).

Thus, the introduction of newer, more potent immunosuppressants over the last 2 decades has significantly reduced the incidence of AREJ. On the one hand the use of more potent immunosuppression is likely to increase the risk of infections and malignancy thereby contributing to excess mortality; however, given the positive association of AREJ with CREJ and chronic graft failure, there is certainly potential for improvement in long-term allograft survival with the appropriate use of the newer immunosuppressant drug combinations. Tailoring therapy by administering more potent immunosuppression to those at higher immunological risk such as HLA-mismatched or pre-sensitised RTx may permit reduction of allograft failure due to immunological mechanisms.

Non-immunological Causes

Apart from surgical causes, there are many pre-transplant donor and recipient factors leading to DGF and chronic allograft failure by non-immunological mechanisms. Shoskes and Cecka[18] reported that even in the absence of early rejection, DGF reduced 1-year graft survival from 91% to 75% (P <0.0001) and graft T1/2 from 12.9 years to 8.0 years in a CAD RTx population. Donor factors such as older age, cause of death due to cerebrovascular accident, history of hypertension and recipient factors such as older age, male gender, increased body mass index and diabetic status all contribute to an excess risk for DGF post-CAD renal transplantation.[19] Unfortunately, many of these pre-transplant donor and recipient variables are largely not modifiable at the time of transplantation. On the other hand, other post-transplant variables which contribute to further damage to donor kidneys may be preventable: increased cold ischaemia time, CNI nephrotoxicity, hypertension, hyperfiltration and nephron injury due to viral infections are important non-immunological factors contributing to chronic allograft failure (Fig. 1).

Cold Ischaemia Time

During organ procurement, the blood supply to the organ is interrupted. This leads to anaerobic metabolism within the cells with loss of energy substrates, reduction of membrane ATPase activity, consequent accumulation of calcium, sodium and water in the cells and subsequent cellular swelling.[20] During reperfusion of the donor organ, hypoxanthine and free radicals that accumulate during the ischaemic period lead to lipid peroxidation of cell membranes and promote cell death through necrosis and apoptosis. Cold ischaemia also leads to disruption of the microtubular network and relocation of membrane-associated cytoskeletal proteins inside tubular cells, thereby causing cellular dysfunction and DGF. Lymphocyte infiltration into the ischaemic kidney then leads to the stimulation of the synthesis of basement membrane and extracellular matrix proteins, such as Type I, III and IV collagens, fibronectins and proteoglycans, which then cause renal interstitial fibrosis, the hallmark of progressive renal damage. As alluded to earlier, lymphocyte infiltration into the ischaemic kidney also exposes the allograft to a higher incidence of AREJ and consequent renal damage.

Calcineurin Inhibitor Nephrotoxicity

Though CNI have been the mainstay of immuno-suppressive therapy in renal transplantation since the 1980s, their use contributes to acute and subacute renal dysfunction or more frequently, chronic allograft dysfunction. The underlying pathophysiology of CNI nephrotoxicity is the altered release of vasoactive substances, such as angiotensin II, endothelin, prostaglandins and nitric oxide, as well as the stimulation of proliferative genes such as transforming growth factor-beta (TGF-b), osteopontin, and Type I and IV collagens. These effects lead histologically to obliterative vasculopathy of the afferent arteriole and tubulointerstitial fibrosis,[21] and lead clinically to decreased glomerular filtration rate, impaired urea excretion, hyperkalaemia, hypertension and tubular dysfunction, and eventually progressive allograft failure. It has been suggested that CNI nephrotoxicity is nearly universal at 10 years among kidney-pancreas transplant recipients receiving continuous CNI therapy.[22]

Hypertension

The prevalence of post-transplant hypertension in CNI-treated renal allograft recipients ranges from 35% to 80%. CNI-mediated increase in sympathetic nervous system activity, renal vasoconstriction and sodium/water retention, renal artery stenosis, increased renin from native kidneys, renal dysfunction *per se*, obesity, smoking and high-salt intake are some of the causes of hypertension in RTx. Similar to the role of hypertension in the development and progression of renal dysfunction in native kidney disease, hypertension post-transplant has been shown to be associated with a poorer graft outcome while antihypertensive therapy has been shown to be associated with improved survival.[23-25] Transmission of systemic pressures to the glomerulus with consequent increase in glomerular capillary wall tension and hypertension, i.e., glomerular hypertension, has been postulated to lead to increased trafficking of macromolecules through the mesangium and mesangial expansion.[25] In fact, glomerular hypertension causes injury to all glomerular cell types and its progression to

glomerulosclerosis is akin to progression of atherosclerosis in systemic hypertension. Increased shear stress on glomerular capillaries, as that occurring with glomerular hypertension, may enhance local release of vasoactive substances and growth factors such as platelet-derived growth factor and TGF-b and lead to platelet adhesion, lipid deposition and glomerular capillary thrombosis, and eventually to glomerular sclerosis. Mesangial cell injury and proliferation secondary to mesangial lipid deposition also contributes to progressive glomerular sclerosis and loss of functioning renal mass.

Hyperfiltration

Regardless of the mechanism of initial renal injury, subsequent progression of renal damage in renal allografts has been attributed to hyperfiltration injury.[26] Hyperfiltration and progressive glomerulosclerosis were first observed in a model of 5/6th nephrectomised rats and were extrapolated to occur in remnant nephrons as a homeostatic adaptation to the progressive loss of nephron mass.[27] Several glomerular haemodynamic changes, such as increases in single nephron glomerular blood flow, sustained elevation of glomerular capillary pressures and glomerular hypertrophy, have been suggested to contribute to glomerulosclerosis in hyperfiltrating nephrons.[26] As suggested by Brenner,[26] the nephron dose transplanted initially may have an impact on chronic allograft failure; subsequent nephron loss due to rejection or other non-immunological mechanisms contribute further to a cycle of hyperfiltration and progressive glomerulosclerosis. Indeed, as demonstrated by Terasaki et al,[28] allograft failure rates are higher in situations in which the nephron dose may be inadequate, as with the use of small kidneys from donors aged 4 to 6, transplants into large recipients (over 100 kg), grafts from females to males as compared with males to females and kidneys that experience rejection episodes.

Other Risk Factors

Other risk factors associated with allograft failure are hyperlipidaemia and viral infections such as those caused by the cytomegalovirus (CMV) and polyoma virus. Though there is some debate regarding the impact of hyperlipidaemia, some studies have demonstrated a correlation with graft failure and of course, patient death.[29] In an analysis of the UNOS database, Fitzgerald et al[30] demonstrated worse patient and graft survivals for CAD RTx recipients who were CMV-seropositive pre-transplant. Though CMV-related interstitial nephritis, CMV glomerular vasculopathy or CMV inclusions within renal allograft have all been reported, CMV infections may cause nephron injury by initiating AREJ or by triggering chronic vascular sclerosis by promoting migration of smooth muscle cells into vessel walls.[31] Polyoma virus infection, or BK virus (BKV) nephropathy, is an increasingly important cause of allograft dysfunction and an important cause of allograft loss in recent years. Though the virus may be present in a quiescent state in over 90% of individuals, immunosuppression exacerbates its propensity to cause disease. In RTx, BKV infection can cause an interstitial nephritis that leads to graft dysfunction or ureteritis and obstruction.[32] Potent combination immunosuppressive regimens utilising TAC and MMF appear to particularly predispose to the development of BK nephropathy.

Strategies to Reduce Non-immunological Graft Loss

From the data presented above, it is apparent that there are many non-immunological causes of allograft failure, each requiring a different approach in prevention or treatment.

Reducing Organ Ischaemia

Though many of the demographic risk factors associated with cold ischaemia cannot be altered, as suggested earlier, opting for LD renal transplantation preferentially over CAD transplantation is associated with a lower risk of organ ischaemia and is likely to contribute to better survival in the former. Minimising hypotension in the donor prior to organ harvest as well as the use of reno-protective preservative solutions and additives during organ storage may prevent the initial injury associated with ischaemia reperfusion injury.[20]

Mitigating CNI Nephrotoxicity

As CNI use appears to be invariably accompanied by renal injury, many approaches have been tried to limit its nephrotoxicity. One approach has been the use of close CsA or TAC level monitoring to achieve therapeutic levels within a window that minimises risk for AREJ and toxicity. However, this approach does not ensure freedom from toxicity due to the narrow therapeutic window of the drugs, and toxicity is often unrelated to levels. Another approach has been the complete withdrawal of CsA. While some studies have demonstrated improved graft survival and renal function in selected RTx populations,[33] other studies have demonstrated an increased incidence of late AREJ and even CREJ or graft loss in withdrawn patients, suggesting that this option is not applicable to all.[1,34] To avoid causing immunological allograft losses whilst preventing CNI-related nephrotoxicity, more recent strategies have focused on efforts to minimise, eliminate or avoid CNI exposure altogether while incorporating potent, non-nephrotoxic immunosuppressants such as mycophenolate or sirolimus as maintenance therapy. Weir et al[35] demonstrated a reduced rate of renal deterioration in RTx recipients who had addition or continuation of MMF together with discontinuation or reduction of CNI. In a

study of conversion from CNI-based to SIR-based maintenance immunosuppression in RTx with renal dysfunction, Citterio[36] demonstrated improved renal function following conversion from CNI to SIR in RTx with renal dysfunction. Randomised clinical trials are in progress to confirm the utility of this approach in ameliorating CNI nephrotoxicity. The final approach is to avoid the use of CNI from the outset and use a CNI-free combination maintenance therapy with SIR, mycophenolate and steroids following induction with anti-lymphocyte antibodies. Using such a regimen, Flechner et al[37] demonstrated an AREJ incidence of 6.4% for the SIR-based regimen (versus 16.6% for CsA-MMF-steroids-IL2rAb, P = NS) with significantly better renal function in the former (1-year creatinine clearance of 81.1 mL/min versus 61.1 mL/min for SIR versus CsA, P = 0.004, respectively).

Antihypertensive Therapy

Any antihypertensive is likely to be effective in treating hypertension in RTx. Furthermore, immunosuppressive drug combinations with mycophenolate or SIR that are CNI-sparing will also ameliorate hypertension and its associated renal injury. A target blood pressure of 130/80 mm Hg, as in the chronic renal failure population, is also likely to be beneficial in retarding progression of chronic allograft failure.

Reducing Hyperfiltration Injury

Prevention of hyperfiltration, particularly in the context of a reduced number of functional nephrons as in RTx, could prolong graft survival after renal transplantation. Angiotensin-converting enzyme (ACE) inhibitors have been convincingly demonstrated to slow the progression of renal failure in native kidney disease, especially in conditions associated with proteinuria. The achieved nephroprotection correlates with the reduction of proteinuria by ACE inhibitor treatment. Treatment with ACE inhibitors or angiotensin receptor blockers (ARB) reduces glomerular capillary pressures and further inhibits mechanisms of injury mediated by glomerular hypertension, hyperfiltration and an activated renin-angiotensin system (RAS).[38] In experimental studies, angiotensin II, by converting latent TGF-b to its biologically active form, may be a growth promoter for vascular smooth muscle cells following vascular injury.[39] In a study comparing the calcium channel blocker, amlodipine, with the ARB, losartan, the latter maintained glomerular function rate, lowered plasma TGF-b levels and was associated with lower endothelin levels and may thus be useful in mitigating hypertension-induced renal injury.[38] ACE inhibitors and ARB may thus be particularly useful in reducing proteinuria and reducing hyperfiltration injury in RTx, and exert beneficial effects on immunologic processes contributing to chronic graft nephropathy.

Mitigating Other Risk Factors

Treatment of hyperlipidaemia in RTx can be expected to reduce the progression of coronary atherosclerosis, and thus decrease cardiac morbidity and mortality as in the normal population. While cardiac death or non-fatal myocardial infarction were reduced following fluvastatin therapy in several low cardiovascular risk subgroups in the Assessment of Lescol in Renal Transplantation (ALERT) Study, there was no reduction in renal functional deterioration at the end of 5 to 6 years of follow-up.[40,41] On the other hand, statins have been demonstrated to reduce AREJ in CAD RTx, an effect attributed to their effects on natural killer cell activity, suggesting that there may be more than one benefit from treating hyperlipidaemia in this population.[42]

As infections are largely related to the net burden of immunosuppression in RTx, their occurrence can be ameliorated by reduction in immunosuppression. Prophylaxis or preemptive therapy of CMV infections with ganciclovir has largely reduced the burden of early CMV disease and its attendant side effects. On the other hand, as there is no effective therapy for BKV nephropathy, judicious use of immunosuppression at the outset is the best protection against its occurrence; once infection has occurred, reduction in immunosuppression or cidofovir therapy may be the only available options.[43]

In summary, as the factors contributing to non-immunological causes of chronic allograft failure are similar to that occurring in native renal disease, strategies similar to that in chronic renal failure such as good control of hypertension and ACE inhibitor or ARB, can ameliorate progression of chronic allograft failure. Furthermore, as non-immmunologic and immunologic toxicities of immunosuppressive drugs contribute to renal damage, tailoring immunosuppression will further mitigate progression of allograft dysfunction.

Combination of Immunological and Non-immunological Causes

As alluded to earlier, both immunological and non-immunological mechanisms of injury may contribute to chronic allograft failure (Fig. 1). For example, DGF *per se* causes graft loss from immunological mechanisms such as AREJ and CREJ, and from non-immunological mechanisms. Furthermore, more than one cause may coexist in the same patient. Similarly, both immunological and non-immunological mechanisms contribute to nephron damage in RTx with recurrence of original disease and in CAN.

Recurrence of Original Disease

Recurrent disease, of both immunologically or non-immunologically mediated diseases, is an important cause of allograft failure. From the Renal Allograft Disease Registry, Hariharan et al[44] demonstrated recurrence in 3.4% of RTx recipients at approximately 1.9% years post-transplant. Those with disease recurrence had an overall 2-fold risk of graft loss, with focal and segmental glomerulonephritis (GN), membranoproliferative GN and haemolytic uraemic syndrome especially being associated with higher risks. Unfortunately, there are no definite parameters to stratify, prior to transplantation, those with GN who are likely to have allograft failure due to recurrence; moreover, therapies for treatment of recurrent GN are also limited. Therefore, preventing allograft failure from recurrent GN is an area for future research, especially with the use of newer immunosuppressants.

Among non-immunological conditions leading to ESRF, diabetic nephropathy (DN) is the leading cause worldwide. Among 81 RTx recipients who had either pre-transplant DN or de novo post-transplant diabetes, DN was detected in the allograft at 6.7 years post-transplant. However, the traditional risk factors for native DN were not evident in this transplant population, suggesting novel mechanisms in its pathogenesis.[45] Nevertheless, as in native DN, strict control of diabetes and hypertension and the use of ACE inhibitors and/or ARB may prevent or slow recurrence.

Chronic Allograft Nephropathy

In the past, the term "chronic rejection'' was applied to this entity; however, it is now clear that following nephron damage from any cause, both immunological and non-immunological mechanisms contribute to progression of renal damage and ultimately culminate in chronic allograft failure and graft loss. Nankivell et al,[22] in a longitudinal analysis of protocol renal biopsies in kidney-pancreas transplants receiving CNI, analysed the prevalence of CAN, as defined by chronic interstitial fibrosis and tubular atrophy, with or without fibrointimal vascular thickening. They demonstrated that subclinical rejection, as defined by histologic findings of AREJ without overt renal functional deterioration, was present in up to 60.8% of RTx recipients 1 month after transplantation, but in only 17.7% of RTx recipients 6 to 10 years post-transplant. They suggested that these immunologic changes subside in the majority with continued CNI-immunosuppression. Furthermore, although subclinical rejection increased the risk of CAN 3.5 times by 1 year, by 10 years, 100% of RTx recipients, even those without prior rejection had CAN at that time. Indeed, the histologic changes of chronic CNI nephrotoxicity were found in 96.8% of RTx recipients 10 years post-RTx. These findings suggest that while CNI therapy initially protects the kidney from immunological injury, these same drugs mediate long-term injury by non-immunological mechanisms.

In summary, nephron injury post-renal transplantation spans a continuum of time that begins prior to organ harvest. Though early post-transplantation, rejection and immunological mechanisms predominate, late injury due to haemodynamic and immunosuppressive drug nephrotoxicity leads to progressive renal damage and late allograft failure. In a second paradigm, while more potent immunosuppressants may reduce the risk of AREJ and thus ameliorate immunological risk factors, viral infections, e.g., CMV and BKV, may be reactivated by excess immunosuppression, thereby enhancing non-immunological risk factors of allograft injury. Optimising each of these time-dependent and immunosuppressive drug-related factors would allow maximisation of renal allograft function and survival. Immunosuppressive strategies that are non-nephrotoxic or are tolerogenic and tailored to the individual will certainly mitigate the immune mechanisms. Finally, therapeutic interventions that have been effective in ameliorating the progression of damage in native renal disease are also likely to be effective in chronic allograft failure. Thus, measures to reduce glomerular and systemic hypertension and those to downregulate the activated RAS are likely to be as important in optimising allograft survival.

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