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Current unmet needs in renal transplantation: a review of challenges and therapeutics

Liron Walsh[1], Rajani Dinavahi[1]

[1]Amgen, Nephrology Therapeutic Area, Thousand Oaks, CA

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1. ABSTRACT

While has been considerable progress in the short-term outcomes following renal transplantation over the last several decades, minimal gains have been made with regards to long-term graft function and patient survival (1). The lack of long-term gains has been attributed to factors such as antibody mediated rejection (AMR), chronic allograft nephropathy (CAN), and toxicity to the allograft secondary to immunosuppression. Ischemia reperfusion injury (IRI) is also thought to contribute to poor long-term graft function, and its impact on patient and graft outcomes will likely expand with the increasing use of marginal kidneys secondary to organ shortages. While patient survival remains far below that of the general population, the causes of death have evolved in recent years with decreases in the rate of death from cardiovascular disease and infection, and increases secondary to malignancy (2), which are largely attributable to the potency of modern immunosuppression. As such, the development of novel therapies which can prevent delayed graft function (DGF), minimize AMR, while simultaneously reducing toxicity is vital to the improvement of long-term graft and patient outcomes.

2. DELAYED GRAFT FUNCTION

2.1. Background

IRI is inevitable during the course of a kidney transplant and is the result of the various stages of the transplant process; injury to the allograft begins with the management of the donor, and continues with organ procurement and transport to implantation. During this process, both cold and warm ischemia and immune-mediated factors (innate and adaptive), may exact deleterious effects on graft function (3). The clinical consequences of IRI are more commonly associated with deceased donor kidney transplantation but may occur in kidneys transplanted from a living donor as well. IRI primary manifests in the immediate post-transplant period as DGF, most commonly defined as the need for hemodialysis in the first week following transplantation, but may rarely result in primary non-function of the transplant (4). Recent studies also demonstrate that DGF can negatively impact the long-term function of the kidney transplant (5,6). As a consequence of expanding the deceased donor pool through the use of marginal kidneys from expanded criteria donation and donation after cardiac death, the rate of DGF has increased (3). Over the last several years, there have been considerable advances in understanding the molecular pathway through which IRI acts, providing the opportunity to develop meaningful therapeutics in order to improve short-term and long-term outcomes of kidney transplantation. A comprehensive review of the clinical consequences, molecular mechanisms and the design of clinical trials to improve rates and consequences

of DGF are presented in this series (see Chun-Cheng Chen, *et al*).

2.2. Treatment and clinical trials for novel therapies

To date, no therapy or treatment-strategy has become standard of care in the prevention or treatment of DGF. In very limited randomized control trials, minor short-term improvements have been demonstrated in the time to recovery in DGF or prevention of DGF with reduced dose cyclosporine (7), and thymoglobulin infused intra-operatively (8). Despite several randomized control trials comparing various preservation solutions, the rate of DGF is similar between Histidine-Tryptophan-Ketoglutarate and University of Wisconsin solutions (9-11). In addition to a lack of short-term improvements, there are no randomized control trials which have demonstrated a survival advantage of the patient or graft, which is of particular importance to the Food and Drug Administration when evaluating potential new therapies (12).

Given the recent advances in elucidating the mechanism of injury in IRI, novel therapeutics are being tested to improve both short-term and long-term outcomes. One such promising therapy is Diannexin which has been shown in animal models to prevent thrombosis and leukocyte recruitment to endothelial cells of an allograft (13). This is accomplished by blocking phosphatidylserine, which is translocated to endothelial cell surfaces secondary to ATP depletion, with subsequent binding of platelets and leukocytes ultimately leading to cellular injury (14). In a multi-center phase 2 clinical trial, Diannexin, administered intravenously 15 minutes following reperfusion of kidney transplants following prolonged ischemia demonstrated statistically improvement in the need and duration for dialysis therapy (15). Despite the early success of Diannexin in preventing DGF, a phase 2/3 study was terminated by the sponsor (clinicaltrials.gov accessed 4/19/2014). Other promising agents under development include I5NP, OPN-305, and eculizumab.

I5NP is an inhibitor of the pro-apoptotic gene p53 which is up-regulated during IRI (16). Inhibition of p53 via small interfering RNA I5NP halts p53 expression and has been shown in animal models of IRI and *in vitro* to prevent apoptosis and protect kidney function (17,18). A phase1/2 study is currently underway examining the safety and efficacy of I5NP to prevent DGF.

OPN-305 is an antibody directed against toll-like receptor 2 (TLR-2). Activation of TLR-2 mediates renal injury by stimulating pro-inflammatory cytokines, such as such as IL-6 and TNF-α (19). OPN-305, a humanized anti TLR-2 antibody and is currently being studied in a phase 2 study to assess the need for dialysis within 7 days following kidney transplantation. Inhibition of TLR-2 was shown to protect renal allografts from injury, as demonstrated by improved histopathologically and renal function, in an animal model of kidney transplantation (20).

Eculizumab is an antibody to the C5 component of the complement cascade, which is thought to contribute to IRI in kidney transplantation through its conversion to C5a. This conversion results in injury to the allograft both directly and via activation of the adaptive immune response (21). Eculizumab was developed and is approved for the treatment of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome (22,23). Eculizumab, has also been used successfully to treat the recurrence of atypical hemolytic-uremic syndrome post-kidney transplantation (24) and for antibody mediated rejection (25). There is evidence that C5a receptor expression is increased in transplanted kidneys following IRI and particularly in those with prolonged cold-ischemia time. In animal models of IRI, blockade of C5a receptor has been shown to attenuate cytokine release and improve kidney function (26). Pilot studies are underway to evaluate the role of eculizumab in the prevention DGF.

While exhibiting promising results in animal models of IRI and transplantation, other therapeutics that have recently been evaluated in randomized placebo-controlled clinical trials to assess immediate graft function following transplantation have failed to demonstrate any benefit in preventing DGF. The list includes YSPSL, and enlimomab (27,28). YSPSL was developed as a recombinant fusion protein designed to inhibit P-selectin. The target, P-selectin, is translocated to endothelial cell surfaces during stress and recruits polymorphonuclear leukocytes. In a phase 2 study, YSPSL, compared to placebo, failed to improve the rates of DGF, defined as the need for HD within the first week post-transplant, and failed to decrease serum creatinine by at least 50% immediately following transplantation. Similarly, enlimomab, a monoclonal antibody against ICAM-1, an inflammatory leukocyte recruitment protein, failed to reduce the risk of DGF or improve the incidence of acute cellular rejection in clinical studies.

The importance of preventing and treating DGF is highlighted in the recent FDA workshop on IRI in kidney transplantation (12). The workshop stressed the need for novel therapeutics to curtail the impact of DGF in the short-term, but also emphasized the need to reduce the rate of discarded organs and improve long-term allograft function.

3. POST-TRANSPLANT MALIGNANCY

3.1. Background

Significant advances, over the last 2 decades, have been made in both short-term graft and patient survival following kidney transplantation, which are largely attributable to the introductionof novel induction

therapies, and calcineurin inhibitors. However, despite these improvements, the life expectancy of kidney transplant recipients still remains reduced compared to the general population in part due to death from malignancies. Depending on the series, malignancy accounts for approximately 10-18% of all patient deaths following kidney transplantation and is the third most common attributable cause of death following cardiovascular disease and infection (U S Renal Data System, USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2013) (29,30). The most common malignancy related deaths are reported to be due to lymphoma and lung cancer (30).

The most common malignancies in the post-transplant period include non-melanoma skin cancer and post-transplant lymphoproliferative disorders (31,32). The cumulative incidence of de-novo malignancies (excluding non-melanoma skin cancer) after 25 years of immunosuppression therapy, in one series, was found to be as high as 40% compared with a rate of 20% in matched controls (33). The risk of acquiring a malignancy is not thought to be increased prior to transplantation (31), and as such, the increased rate is likely due to immunosuppression and the types of agents used. In fact, in one analysis, the risk of malignancy post-transplantation is on-par to that experienced in patients with HIV and attributable in part to immune deficiency post-transplantation (34).

Specifically, with regards to the type of immunosuppression agents, the risk of malignancy in the post-transplant period has been shown to be increased with the introduction of more modern immunosuppressive agents, such as calcineurin inhibitors (CNI), though the increased risk has not been observed with the use of mTOR-inhibitor (mammalian target of rapamycin) based therapies nor with mycophenolate mofetil (MMF) (33). Due to the increased potency of CNIs compared with older generation immunosuppressive agents such as azathioprine, there is a resulting decreased ability of the immune system to recognize and eliminate cancer-specific antigens as well oncogenic viruses (35). Additionally, CNIs have been shown to promote tumor growth through vascular endothelial growth factor, decreased DNA repair and by cytokines which can promote B-cell activation (36). Unlike CNIs, mTOR-inhibitors, everolimus and sirolimus, have anti-tumorigenic properties and have been associated with a decreased risk of de-novo malignancies when used as a first-line agent (37) as well as after withdrawal of CNIs (38). mTOR-inhibitors exhibit their anti-neoplastic properties through inhibition of oncogenic signaling (39). Despite the anti-tumor properties, mTOR-inhibitors are likely best reserved for those at high risk of developing cancer, as they are also associated with increased rates of acute cellular rejection and graft loss (40), in addition to poor wound healing and dyslipidemia (41). The data with regards to MMF, an inhibitor of lymphocyte proliferation initially developed as an anti-neoplastic agent, suggests that there is a decreased incidence of malignancy compared with azathioprine (35). Indeed, *in vitro* experimentation has demonstrated that MMF inhibits various tumor cell-lines (42).

In addition to the increased risk of malignancy with CNIs, the risk of post-transplant lymphoproliferative disorder (PTLD) is also increased with the use of lymphocyte-depleting induction therapy (35) such as rabbit and equine anti-thymocyte globulins. This risk is highest in the first year following induction and with use of higher doses of CNIs for immunosuppression (43). The risk of PTLD with the use of lymphocyte-depleting induction therapy is thought to be related to the unrestricted proliferation of B-cells infected by Epstein-Barr virus, which is commonly reactivated early in the post-transplant setting as a result of immunosuppression (44). Unlike more traditional induction agents such as anti-thymocyte globulins, IL-2 receptor antagonists (basiliximab) are not associated with an increased risk of malignancy (33). Despite this potential benefit of basiliximab, studies have demonstrated an increased risk of acute rejection, graft loss and death (45) compared with rabbit anti-thymocyte globulin. Additionally, there is the potential for an increased risk of antibody mediated rejection and de-novo donor-specific antibodies (46).

3.2. Treatment and clinical trials for novel therapies

Treatment of post-transplant malignancies often involves decreasing, discontinuing or substituting immunosuppressive therapies, thereby increasing the risk of graft loss from inadequate immunosuppression. Additional risks to the graft thereafter include nephrotoxic chemotherapeutic agents. Minimizing the risk of post-transplant malignancy should therefore be a key consideration when selecting an immunosuppressive regimen.

Currently, there are no on-going clinical trials examining the impact of novel immunosuppression therapy and the development of a post-transplant malignancy. Given the impact of malignancy on patient survival, tailoring the intensity of immunosuppression based on the risk of malignancy, in addition to developing novel immunosuppressive regimens, and immunological monitoring, are key components to the future prevention.

4. ANTIBODY-MEDIATED REJECTION

4.1. Background

Over 14,000 kidney transplants are performed annually in the US (www.kidney.org). Overall 1-and

5-allograft survival rates are approximately 90 and 70% (www.unos.org). Improvements in immunosuppression therapies have drastically reduced acute rejection rates in renal transplantation and increased graft survival at 1-year (47). Rejection episodes are classified as acute or chronic and cellular or antibody mediated. Rejection episodes are generally classified into T-cell (cellular), B-cell (antibody) mediated, or mixed processes. Current induction and maintenance immunosuppressive therapies predominantly target T-cell immune responses, and thus, 1-year acute rejection rates have declined to 10% (www.unos.org). Antibody mediated rejection, however remains an important unmet need in transplantation and an area of ongoing research.

Antibody mediated rejection (AMR) is a significant risk factor for poor outcomes following transplantation, and is associated with increased mortality as well as graft loss (48). Risk factors for the development of antibodies and subsequently AMR include pregnancy, blood transfusion, and previous transplantation (49). While AMR episodes are relatively rare overall following kidney transplantation, the incidence exceeds 25% among highly sensitized patients (50,51).

Antibody mediated rejection is typically classified by the temporal relationship to organ transplantation. Hyperacute AMR, usually occurs within hours of receiving a transplant occurs as a result of high-titer, pre-formed antibodies, isohemagglutinins, or anti-endothelial cell antibodies and results in irreversible injury and allograft loss (52). Such severe, early rejection rarely occurs due to improvements in antibody testing (52). Acute antibody mediated rejection is associated with anti-HLA anitbodies and can occur at any time point post-transplantation, although it usually occurs early after transplantation (53). Chronic AMR is particularly problematic and seems to be associated with Class II donor specific antibodies (54). Reversibility of late antibody mediated rejection is also difficult, as lab monitoring generally decreases at this point post-transplant at which point the process is advanced.

4.2. Treatment and clinical trials for novel therapies

The mainstay of therapy for pretransplant desensitization as well for antibody mediated rejection has been aimed at ablating B cell responses or removing antibodies. Plasmapheresis or immunoadsorption, and intravenous immunoglobulin (IVIG) have been frequently used for removal of circulating HLA antibodies (55-58). Plasmapheresis non-specifically removes high molecular weight proteins, clotting factors, and complement components. Immunoadsorption is a selective technique where immunoglobulins are removed using a staphylococcal protein A column. The immunomodulatory effects of IVIG include engagement of anti-idiotypic networks, complement cascade blockade, inhibition of T and B cell function and modulation of pro-inflammatory cytokines and the effect is longer lasting than that of plasmapheresis (59,60). Both therapies are generally well tolerated, with mainly few hematologic side effects.

Additional adjunctive therapies which have been used for the treatment of AMR (for a detailed review on the pathophysiology and treatment of AMR, please refer attached article (Sandal *et al*), most notably include anti-CD20 monoclonal antibodies, proteasome and complement inhibitor based therapies. Rituximab, is a high affinity, chimeric humanized mouse anti-human CD20 mAb which reduces B-cell precursors responsible for clonal expansion during AMR. Importantly, it does not remove antibody-producing plasma cells. Bortezomib, a proteosome inhibitor, is used to treat plasma cell neoplasms and has potent anti-apoptotic activity on rapidly dividing cells. As such, it has been used as a primary as well as adjunctive therapy for acute AMR, in addition to IVIG and plasmapheresis based protocols (61,62). Eculizumab, is a humanized monoclonal antibody which binds complement protein C5, inhibiting the terminal complement pathway and has been reported to decrease antibody mediated rejection in sensititized renal transplant recipients (63).

A Summary of FDA Antibody Mediated Rejection Workshop was published in the American Journal of Transplantation in 2011. The report highlighted the need to study AMR given the high risk of associated allograft loss, and the fact that no FDA approved therapy exists for the treatment of AMR. The report further discussed the difficulty in systematically conducting randomized controlled clinical trials to study AMR. The difficulty in conducting trials was attributed to a variety of factors, including that methods to characterize alloantibodies have not been standardized across transplant centers. Flow based bead assays have an inherent heterogeneity in antibody measurement due to differences in the amount of coated antigen on beads from different lots, and thus the interpretation may be qualitative and semi-quantitative (64). Interpretation of the clinical significance in titer of those antibodies as well the effect of therapeutic interventions is difficult when comparing across patients and centers. In fact, no flow based assessment of alloantibodies has been FDA approved; however, such flow based assessments have become the standard of care at many centers. Further, histologic classification and diagnosis of AMR can also be different across center specific staining methods for C4d. Finally, while positive short term outcomes have been reported with treatment, the majority of studies are small numbers of patients and uncontrolled with significant heterogeneity in the treatment regimens. Long term studies providing support for treatment have largely not been conducted (65). Reasonable clinical endpoints which predict clinical benefit also need to be

clearly defined, such as glomerular filtration rate (GFR), DSA and histology (65).

5. CHRONIC ALLOGRAFT NEPHROPATHY AND TRANSPLANT GLOMERULOPATHY

5.1. Background

While 1-year allograft survival has substantially improved, long term allograft survival has remained relatively unchanged over the last three decades (66). Chronic allograft nephropathy (CAN) remains the most common cause of renal allograft loss, and severe CAN is present in almost 60% of allografts at 10-years post-transplant (67). As many as 40% of allografts have dysfunction and eventually fail within 10-years post-transplant (68,69). Chronic allograft nephropathy was classically characterized by a deterioration in renal function, interstititial fibrosis and tubular atrophy that leads to proteinuria, elevated blood pressure, and increases in serum creatinine. Early immunologic injury followed by non-immunologic injury contribute to its development, however, the etiology of CAN is not very well understood and represents a histologic rather than pathophysiologic diagnosis. Previously referred to as chronic rejection, the nomenclature has evolved to specify the etiology of allograft injury. The Banff '05 meeting report separated CAN into immunologic and non-immunologic causes and specifically grouped CAN into active chronic allograft rejection (both T-cell and antibody mediated), non-rejection infectious (infection, structurally mediated injury, hypertension, diabetes, drug toxicity), and non-specific cause (70).

CAN pathology progresses over time (71). Immunologic and non-immunologic factors play a role. Immunologic risk factors for the development of chronic allograft injury include multiple, late (>3 months) episodes of acute rejection, subclinical rejection, presence of anti-HLA antibodies, and episodes of antibody mediated rejection (67,72-75). Non-immunologic factors include donor and recipient age, prolonged cold ischemic time, as well as underlying medical conditions in the recipient such as hypertension, hyperlipidemia, and proteinuria (71). The type of immunosuppressive medication has also been correlated with CAN (67,76-78).

Immune mediated allograft injury can be classified into T-cell or antibody mediated processes and predominates early post-transplantation (67). Chronic antibody based injury is believed to be at least partially complement mediated, leading to persistent endothelial cell damage (53,79).

5.2. Treatment and clinical trials for novel therapies

By 10 years post transplantation >60% of allografts exhibit evidence of severe CAN (67). Early intervention strategies have predominated the therapeutic landscape. The advent of calcineurin inhibitors has greatly decreased the risk of acute rejection, however, by 10 years post-transplantation, almost all protocol renal biopsies demonstrate evidence of cyclosporine toxicity (77). Studies of recipients of organs other than kidneys show a 16.5% risk of development of chronic kidney disease after 36 months. This risk is associated with hypertension, hepatitis C infection, and increasing age, among other factors (80). CNI toxicity is the most common cause of renal impairment, as evidenced by the number of patients requiring dialysis after organ transplants other than kidney and the correlation between high calcineurin inhibitor levels and degree of CAN. This is readily evidenced by a 2010 study where heart and lung transplant recipients had a >60% rate of arteriolar hyalinosis (81). Long term follow-up data from the ANZDATA registry demonstrated a longer mean graft survival with short-term CsA followed by azathioprine and prednisolone, compared to continuous azathioprine and prednisolone or continuous CsA respectively, a reflection that reduced exposure to calcineurin inhibitors may have a beneficial effect on the development of CAN (82).

Tacrolimus has largely replaced cyclosporine and most centers currently use tacrolimus in combination with mycophenolate mofetil with or without steroids as part of maintenance immunosuppression in the US. Tacrolimus and mycophenolate mofetil in combination have been associated with a better profile for the prevention of acute rejection (83). Naesens published a 2007 study of 239 protocol biopsies of 120 renal transplant recipients treated with TAC, MMF and CS. Biopsy proven early rejection episodes and lower TAC levels were correlated with higher chronicity scores following transplantation, suggesting an early immunologic component to injury in this study (84). Tacrolimus therapy has been demonstrated to result in relatively decreased allograft fibrosis compared to CYA based regimen at 1 year (85). In contrast, two large studies show no difference based on the type of calcineurin inhibitor used. Multi-variate analyses conducted by the USRDS in 9449 patients demonstrated comparable graft survival regardless of cyclosporine vs tacrolimus based therapies (86). Similar results were obtained by the FK506 Kidney Transplant Study Group in 144 patients studied (78). In any case, evidence of calcineurin inhibitor toxicity is universal within a short time following transplantation.

MMF has largely replaced azathioprine as a maintenance immunosuppressive agent due to its improved rejection profile and is now universally part of clinical care. The mechanism of action of this drug is by inhibition of inosine monophosphate dehydrogenase (IMPDH). MMF has an anti-proliferative effect which has been thought to be useful in preventing scars associated with CAN, in addition to anti-proliferative effects as well

as enhanced apoptosis of T cells and reduce antibody production by B cells.

The effect of newer agents, particularly everolimus (proliferation signal inhibitors), as part of calcineurin-inhibitor sparing strategies, are being investigated on nephrotoxicity and renal function in combination with low dose cyclosporine in several global clinical trials (see clinical trials, below). Early reports using sirolimus with cyclosporine reflected a lower incidence of acute rejection episodes compared with cyclosporine in combination with azathioprine and corticosteroids, however, later reports showed a higher incidence of poorer long term allograft survival and renal dysfunction when cyclosporine or tacrolimus were used in combination with mycophenolate mofetil and corticosteroids (87-90). The use of everolimus in an attempt to minimize CNI use is also being studied (see clinical trials, below).

In addition to the immunosuppression therapies described above to aid in the prevention of CAN through the prevention of rejection episodes, angiotensin II converting enzyme inhibitors (ACE-inhibitors) and angiotensin receptor blockers (ARBs) have been studied in the context of chronic allograft nephropathy. ACE-inhibitors and ARBs have been shown to reduce proteinuria and slow the progression of kidney disease in diabetic (91) and non-diabetic patients (92) with chronic kidney disease. Notably, a large meta-analysis of 21 trials with over 1500 patients followed for a median of 27 months concluded that ACE-inhibitor or ARB use results in clinically important reductions in proteinuria and glomerular filtration rate in renal transplant recipients (93). While there are reasonable short term outcomes data with respect to improvement in proteinuria, longer term data with respect to outcomes on long term allograft survival are lacking in the kidney transplant population.

A review of pharmaceutical industry and NIH sponsored studies revealed multiple open interventional studies which are recruiting for the treatment of chronic allograft nephropathy. These studies can be classified into induction studies, evaluating the use of particular induction agents (ie ATG or basiliximab and rituxan, clinical trial identifier NCT00476164, NCT00724022) on the development of CAN; conversion or comparator studies evaluating calcineurin inhibitor minimization or replacement strategies, namely via the use of everolimus (Clinical Trials Identifier NCT01950819). An additional two interventional studies are investigating the use of prostaglandin I2 on the development of CAN, and the effect of rituximab on renal function and proteinuria associated with C4d+ chronic renal allograft rejection. Multiple trials seek to understand the pathophysiology of CAN and to assess biomarkers which herald the development of this lesion, which could potentially permit more targeted therapies (www.clinicaltrials.gov).

6. TRANSPLANT GLOMERULOPATHY

6.1. Background

Chronic active antibody mediated injury is referred most commonly as transplant glomerulopathy and occurs in approximately 15% of renal allografts (94) with CAN and 20% of renal allografts overall by 5 years post transplantation. This diagnosis carries a poor prognosis leading to allograft loss in >30% of cases within 5 years of transplantation (54). This lesion is characterized by glomerular basement membrane duplication and expansion of the lamina rara interna without immune complex deposits (70,79,95). The pathogenesis of TGP is unclear, but, given the strong association with anti-HLA antibodies and positive C4d staining of the allograft with this lesion in a variety of reports, investigators hypothesize immune-mediated mechanisms to play a prominent role (79). C4d is a fragment of the classical complement pathway component C4 and remains stable in peritubular capillaries by covalent binding to the tissue. TG is largely believed to be a complement mediated process and is characterized by the presence or absence of C4d, a breakdown product of the classical complement pathway, although the absence of C4d could still imply antibody mediated injury, as it may have been present prior to sampling. Risk factors for the development of TG include presence of HLA antibodies, previous episodes of AMR, Hepatitis C seropositivity, as well as HLA incompatible transplantation (96). The most closely associated risk factor is the presence of HLA Class I and Class II antibodies (96). Up to 60% of cases of transplant glomerulopathy are not associated with the presence of anti-HLA antibodies (97). Antibodies targeting kidney antigens have been correlated with this lesion (98,99).

6.2. Treatment and clinical trials for novel therapies

Long term allograft survival remains limited in those with transplant glomerulopathy (54,100). No specific form of treatment exists for the treatment of TG. In addition to intensification of immunosuppression to prevent antibody mediated rejection, immunomodulatory therapies have also been implemented to treat TG. Intravenous immunoglobulin, plasmapheresis, immunoadsorption, splenectomy, and rituximab have all been used to treat TG, although the evidence is largely from uncontrolled studies (101). Early detection and prevention are required for optimal outcomes.

Several agents are being investigated for the treatment or prevention of TG. The effect of bortezomib, a proteasome inhibitor used for the treatment of multiple myeloma, is being studied in the area of TG (Clinical Trial Identifier NCT01349595). Endpoints include graft survival, reduction in glomerular filtration rate, as well as reduction in donor specific antibodies after transplant. The efficacy and safety of Eculizumab, a terminal

complement inhibitor currently approved for the treatment of paroxysmal nocturnal hemoglobinuria, is being studied on the incidence of subclinical antibody mediated rejection in sensitized kidney transplant patients (Clinical Trials Identifier NCT02113891). The effect of rituximab, an antibody targeting CD20 on B cells, on C4d+ chronic humoral rejection is also being studied. An additional Phase 4 study using Acthar, a peptide natural form of adrenocorticotropic hormone, is being planned as rescue therapy in adults with an established diagnosis of TG who have failed other therapies and are maximized on an immunosuppressive regimen (Clinical Trials Identifier NCT02057523).

7. CONCLUSIONS

While recent advances in immunosuppressive medications and antibody testing have significantly reduced acute rejection rates, longer term antibody mediated injury and complications of immunosuppression, including post-transplant malignancy and infection remain unmet needs in this field. Few novel therapies have been added into the armamentarium of the transplant physician with an impact comparable to that of calcineurin inhibitors. Expansion of the donor pool through the employment of enhanced immunosuppressive regimens has led to the successful use of incompatible organs; however, delayed graft function and antibody mediated injury have become more prevalent with the use of expanded criteria donor kidney and HLA and ABO incompatible transplantation. Calcineurin inhibitor sparing and minimization strategies are being studied in the context of clinical trials to limit the long term consequences of immunosuppressive therapies both on CAN as well as post-transplant malignancy. The effect of additional therapies, including belatacept, rituxan, and eculizumab are being evaluated on delayed graft function, antibody mediated injury and chronic allograft nephropathy. With a limited number of organs available for donation and transplantation, understanding additional means for expanding the donor pool through enhanced immunomodulatory therapies and prolonging allograft half-life by treating immune mediated injury is essential.

8. ACKNOWLEDGEMENTS

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9. REFERENCES

1. Meier-Kriesche, H U, J D Schold and B Kaplan: Long-term renal allograft survival: have we made significant progress or is it time to rethink our analytic and therapeutic strategies? *Am J Transplant*, 4(8), 1289-95 (2004) DOI: 10.1111/j.1600-6143.2004.00515.x
2. J. Snyder, A M, S. Leppke, A. Israni, B. Kasiske: Causes of Kidney Allograft Loss and Death in the United States, 2000-2010. In: *American Transplant Congress*. Seattle, Wa (2013)
3. Siedlecki, A, W Irish and D C Brennan: Delayed graft function in the kidney transplant. *Am J Transplant*, 11(11), 2279-96 (2011) DOI: 10.1111/j.1600-6143.2011.03754.x
4. Phelan, P J, P O'Kelly, M Tarazi, N Tarazi, M R Salehmohamed, D M Little, C Magee and P J Conlon: Renal allograft loss in the first post-operative month: causes and consequences. *Clin Transplant*, 26(4), 544-9 (2012) DOI: 10.1111/j.1399-0012.2011.01581.x
5. Legendre, C, G Canaud and F Martinez: Factors influencing long-term outcome after kidney transplantation. *Transpl Int*, 27(1), 19-27 (2014) DOI: 10.1111/tri.12217
6. Ponticelli, C, M Villa, B Cesana, G Montagnino and A Tarantino: Risk factors for late kidney allograft failure. *Kidney Int*, 62(5), 1848-54 (2002)
7. Michael, H J, G C Francos, J F Burke, A Besarab, M Moritz, D Gillum and B Jarrell: A comparison of the effects of cyclosporine versus antilymphocyte globulin on delayed graft function in cadaver renal transplant recipients. *Transplantation*, 48(5), 805-8 (1989) DOI: 10.1097/00007890-198911000-00016
8. Goggins, W C, M A Pascual, J A Powelson, C Magee, N Tolkoff-Rubin, M L Farrell, D S Ko, W W Williams, A Chandraker, F L Delmonico, H Auchincloss and A B Cosimi: A prospective, randomized, clinical trial of intraoperative versus postoperative Thymoglobulin in adult cadaveric renal transplant recipients. *Transplantation*, 76(5), 798-802 (2003) DOI: 10.1097/01.TP.0000081042.67285.91
9. Agarwal, A, P Murdock and J A Fridell: Comparison of histidine-tryptophan ketoglutarate solution and University of Wisconsin solution in prolonged cold preservation of kidney allografts. *Transplantation*, 81(3), 480-2 (2006) DOI: 10.1097/01.tp.0000196724.89757.79
10. Lynch, R J, J Kubus, R H Chenault, S J

Pelletier, D A Campbell and M J Englesbe: Comparison of histidine-tryptophan-ketoglutarate and University of Wisconsin preservation in renal transplantation. *Am J Transplant*, 8(3), 567-73 (2008)
DOI: 10.1111/j.1600-6143.2007.02065.x

11. Klaus, F, D B Castro, C M Bittar, A E Bittar, E Keitel, D C Seelig, J C Goldani, M H Meinne and V D Garcia: Kidney transplantation with Belzer or Custodiol solution: a randomized prospective study. *Transplant Proc*, 39(2), 353-4 (2007)
DOI: 10.1016/j.transproceed.2007.01.009

12. Cavaille-Coll, M, S Bala, E Velidedeoglu, A Hernandez, P Archdeacon, G Gonzalez, C Neuland, J Meyer and R Albrecht: Summary of FDA workshop on ischemia reperfusion injury in kidney transplantation. *Am J Transplant*, 13(5), 1134-48 (2013)
DOI: 10.1111/ajt.12210

13. Wever, K E, F A Wagener, C Frielink, O C Boerman, G J Scheffer, A Allison, R Masereeuw and G A Rongen: Diannexin protects against renal ischemia reperfusion injury and targets phosphatidylserines in ischemic tissue. *PLoS ONE [Electronic Resource]*, 6(8), e24276 (2011)
DOI: 10.1371/journal.pone.0024276

14. Neidlinger, N A, E R Hirvela, R A Skinner, S K Larkin, A H Harken and F A Kuypers: Postinjury serum secretory phospholipase A2 correlates with hypoxemia and clinical status at 72 hours. *Journal of the American College of Surgeons*, 200(2), 173-8 (2005)
DOI: 10.1016/j.jamcollsurg.2004.10.010

15. Cooper M, K S, Stratta R: Diannexin, a novel ischemia/reperfusion therapeutic agent, reduces delayed graft function (DGF) in renal transplant recipients from marginal donors. *Am J Transplant*, 10(suppl 4):83. Abstract 145 (2010)

16. Fujino, T, S Muhib, N Sato and N Hasebe: Silencing of p53 RNA through transarterial delivery ameliorates renal tubular injury and downregulates GSK-3beta expression after ischemia-reperfusion injury. *American Journal of Physiology - Renal Physiology*, 305(11), F1617-27 (2013)
DOI: 10.1152/ajprenal.00279.2013

17. Record Owner, N L M: P53 mediates the apoptotic response to GTP depletion after renal ischemia-reperfusion: protective role of a p53 inhibitor

18. Molitoris, B A, P C Dagher, R M Sandoval, S B Campos, H Ashush, E Fridman, A Brafman, A Faerman, S J Atkinson, J D Thompson, H Kalinski, R Skaliter, S Erlich and E Feinstein: siRNA targeted to p53 attenuates ischemic and cisplatin-induced acute kidney injury. *Journal of the American Society of Nephrology*, 20(8), 1754-64 (2009)
DOI: 10.1681/ASN.2008111204

19. Arslan, F, B Keogh, P McGuirk and A E Parker: TLR2 and TLR4 in ischemia reperfusion injury. *Mediators of Inflammation*, 2010, 704202 (2010)

20. Record Owner, N L M: Inhibition of TLR2 promotes graft function in a murine model of renal transplant ischemia-reperfusion injury.

21. de Vries, D K, P van der Pol, G E van Anken, D J van Gijlswijk, J Damman, J H Lindeman, M E Reinders, A F Schaapherder and C Kooten: Acute but transient release of terminal complement complex after reperfusion in clinical kidney transplantation. *Transplantation*, 95(6), 816-20 (2013)
DOI: 10.1097/TP.0b013e31827e31c9

22. Kelly, R J, A Hill, L M Arnold, G L Brooksbank, S J Richards, M Cullen, L D Mitchell, D R Cohen, W M Gregory and P Hillmen: Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival. *Blood*, 117(25), 6786-92 (2011)
DOI: 10.1182/blood-2011-02-333997

23. Tanimoto, T, Y Oshima and M Kami: Eculizumab in atypical hemolytic-uremic syndrome. *New England Journal of Medicine*, 369(14), 1378-9 (2013)

24. Zuber, J, M Le Quintrec, S Krid, C Bertoye, V Gueutin, A Lahoche, N Heyne, G Ardissino, V Chatelet, L H Noel, M Hourmant, P Niaudet, V Fremeaux-Bacchi, E Rondeau, C Legendre, C Loirat and H U S French Study Group for Atypical: Eculizumab for atypical hemolytic uremic syndrome recurrence in renal transplantation. *American Journal of Transplantation*, 12(12), 3337-54 (2012)
DOI: 10.1111/j.1600-6143.2012.04252.x

25. Kocak, B, E Arpali, E Demiralp, B Yelken, C

Karatas, S Gorcin, N Gorgulu, M Uzunalan, A Turkmen and M Kalayoglu: Eculizumab for salvage treatment of refractory antibody-mediated rejection in kidney transplant patients: case reports. *Transplantation Proceedings*, 45(3), 1022-5 (2013)
DOI: 10.1016/j.transproceed.2013.02.062

26. Lewis, A G, G Kohl, Q Ma, P Devarajan and J Kohl: Pharmacological targeting of C5a receptors during organ preservation improves kidney graft survival. *Clin Exp Immunol*, 153(1), 117-26 (2008)
DOI: 10.1111/j.1365-2249.2008.03678.x

27. Gaber, A O, S Mulgaonkar, B D Kahan, E S Woodle, R Alloway, I Bajjoka, S Jensik, G B Klintmalm, P R Patton, A Wiseman, G Lipshutz, J Kupiec-Weglinski, L W Gaber, E Katz, W Irish, E C Squiers and S Hemmerich: YSPSL (rPSGL-Ig) for improvement of early renal allograft function: a double-blind, placebo-controlled, multi-center Phase IIa study. *Clin Transplant*, 25(4), 523-33 (2011)
DOI: 10.1111/j.1399-0012.2010.01295.x

28. Salmela, K, L Wramner, H Ekberg, I Hauser, O Bentdal, L E Lins, H Isoniemi, L Backman, N Persson, H H Neumayer, P F Jorgensen, C Spieker, B Hendry, A Nicholls, G Kirste and G Hasche: A randomized multicenter trial of the anti-ICAM-1 monoclonal antibody (enlimomab) for the prevention of acute rejection and delayed onset of graft function in cadaveric renal transplantation: a report of the European Anti-ICAM-1 Renal Transplant Study Group. *Transplantation*, 67(5), 729-36 (1999)
DOI: 10.1097/00007890-199903150-00015

29. U.S. Renal Data System, USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States In, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD (2013)

30. Farrugia, D, S Mahboob, J Cheshire, I Begaj, S Khosla, D Ray and A Sharif: Malignancy-related mortality following kidney transplantation is common. *Kidney Int* (2013)

31. Kasiske, B L, J J Snyder, D T Gilbertson and C Wang: Cancer after kidney transplantation in the United States. *Am J Transplant*, 4(6), 905-13 (2004)
DOI: 10.1111/j.1600-6143.2004.00450.x

32. Sampaio, M S, Y W Cho, Y Qazi, S Bunnapradist, I V Hutchinson and T Shah: Posttransplant malignancies in solid organ adult recipients: an analysis of the U.S. National Transplant Database. *Transplantation*, 94(10), 990-8 (2012)
DOI: 10.1097/TP.0b013e318270bc7b

33. Wimmer, C D, M Rentsch, A Crispin, W D Illner, H Arbogast, C Graeb, K W Jauch and M Guba: The janus face of immunosuppression - de novo malignancy after renal transplantation: the experience of the Transplantation Center Munich. *Kidney Int*, 71(12), 1271-8 (2007)
DOI: 10.1038/sj.ki.5002154

34. Grulich, A E, M T van Leeuwen, M O Falster and C M Vajdic: Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet*, 370(9581), 59-67 (2007)
DOI: 10.1016/S0140-6736(07)61050-2

35. Gutierrez-Dalmau, A and J M Campistol: Immunosuppressive therapy and malignancy in organ transplant recipients: a systematic review. *Drugs*, 67(8), 1167-98 (2007)
DOI: 10.2165/00003495-200767080-00006

36. Guba, M, C Graeb, K W Jauch and E K Geissler: Pro- and anti-cancer effects of immunosuppressive agents used in organ transplantation. *Transplantation*, 77(12), 1777-82 (2004)
DOI: 10.1097/01.TP.0000120181.89206.54

37. Kauffman, H M, W S Cherikh, Y Cheng, D W Hanto and B D Kahan: Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of de novo malignancies. *Transplantation*, 80(7), 883-9 (2005)
DOI: 10.1097/01.TP.0000184006.43152.8D

38. Schena, F P, M D Pascoe, J Alberu, M del Carmen Rial, R Oberbauer, D C Brennan, J M Campistol, L Racusen, M S Polinsky, R Goldberg-Alberts, H Li, J Scarola, J F Neylan and C T S G Sirolimus: Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial. *Transplantation*, 87(2), 233-42 (2009)
DOI: 10.1097/TP.0b013e3181927a41

39. Luan, F L, M Hojo, M Maluccio, K Yamaji and M Suthanthiran: Rapamycin blocks tumor progression: unlinking immunosuppression

from antitumor efficacy. *Transplantation*, 73(10), 1565-72 (2002)
DOI: 10.1097/00007890-200205270-00008

40. Glotz, D, B Charpentier, D Abramovicz, P Lang, L Rostaing, G Rifle, Y Vanrenterghem, F Berthoux, B Bourbigot, M Delahousse, J M Chalopin, E Cassuto and N Lefrancois: Thymoglobulin induction and sirolimus versus tacrolimus in kidney transplant recipients receiving mycophenolate mofetil and steroids. *Transplantation*, 89(12), 1511-7 (2010)
DOI: 10.1097/TP.0b013e3181db09e4

41. Kaplan, B, Y Qazi and J R Wellen: Strategies for the management of adverse events associated with mTOR inhibitors. *Transplant Rev (Orlando)* (2014)

42. Tressler, R J, L J Garvin and D L Slate: Anti-tumor activity of mycophenolate mofetil against human and mouse tumors in vivo. *Int J Cancer*, 57(4), 568-73 (1994)
DOI: 10.1002/ijc.2910570421

43. Opelz, G and B Dohler: Lymphomas after solid organ transplantation: a collaborative transplant study report. *Am J Transplant*, 4(2), 222-30 (2004)
DOI: 10.1046/j.1600-6143.2003.00325.x

44. Bakker, N A and G W van Imhoff: Post-transplant lymphoproliferative disorders: from treatment to early detection and prevention? *Haematologica*, 92(11), 1447-50 (2007)
DOI: 10.3324/haematol.11272

45. Brennan, D C and M A Schnitzler: Long-term results of rabbit antithymocyte globulin and basiliximab induction. *N Engl J Med*, 359(16), 1736-8 (2008)
DOI: 10.1056/NEJMc0805714

46. Brokhof, M M, H W Sollinger, D R Hager, B L Muth, J D Pirsch, L A Fernandez, J M Bellingham, J D Mezrich, D P Foley, A M D'Alessandro, J S Odorico, M A Mohamed, V Vidyasagar, T M Ellis, D B Kaufman and A Djamali: Antithymocyte globulin is associated with a lower incidence of de novo donor-specific antibodies in moderately sensitized renal transplant recipients. *Transplantation*, 97(6), 612-7 (2014)
DOI: 10.1097/TP.0000000000000031

47. Hariharan, S, C P Johnson, B A Bresnahan, S E Taranto, M J McIntosh and D Stablein: Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Engl J Med*, 342(9), 605-12 (2000)
DOI: 10.1056/NEJM200003023420901

48. Montgomery, R A, M A Hardy, S C Jordan, L C Racusen, L E Ratner, D B Tyan, A A Zachary, r Antibody Working Group on the diagnosis, r risk assessment for antibody-mediated and p desensitization: Consensus opinion from the antibody working group on the diagnosis, reporting, and risk assessment for antibody-mediated rejection and desensitization protocols. *Transplantation*, 78(2), 181-5 (2004)
DOI: 10.1097/01.TP.0000129256.84027.D6

49. Nair, N, T Ball, P A Uber and M R Mehra: Current and future challenges in therapy for antibody-mediated rejection. *J Heart Lung Transplant*, 30(6), 612-7 (2011)
DOI: 10.1016/j.healun.2011.02.002

50. Amico, P, G Honger, M Mayr, J Steiger, H Hopfer and S Schaub: Clinical relevance of pretransplant donor-specific HLA antibodies detected by single-antigen flow-beads. *Transplantation*, 87(11), 1681-8 (2009)
DOI: 10.1097/TP.0b013e3181a5e034

51. Gloor, J M, J L Winters, L D Cornell, L A Fix, S R DeGoey, R M Knauer, F G Cosio, M J Gandhi, W Kremers and M D Stegall: Baseline donor-specific antibody levels and outcomes in positive crossmatch kidney transplantation. *Am J Transplant*, 10(3), 582-9 (2010)
DOI: 10.1111/j.1600-6143.2009.02985.x

52. Patel, R and P I Terasaki: Significance of the positive crossmatch test in kidney transplantation. *N Engl J Med*, 280(14), 735-9 (1969)
DOI: 10.1056/NEJM196904032801401

53. Akalin, E and B Watschinger: Antibody-mediated rejection. *Semin Nephrol*, 27(4), 393-407 (2007)
DOI: 10.1016/j.semnephrol.2007.05.001

54. Issa, N, F G Cosio, J M Gloor, S Sethi, P G Dean, S B Moore, S DeGoey and M D Stegall: Transplant glomerulopathy: risk and prognosis related to anti-human leukocyte antigen class II antibody levels. *Transplantation*, 86(5), 681-5 (2008)
DOI: 10.1097/TP.0b013e3181837626

55. Gloor, J M, S R DeGoey, A A Pineda, S B Moore, M Prieto, S L Nyberg, T S Larson, M D Griffin, S C Textor, J A Velosa, T R Schwab, L A Fix and M D Stegall: Overcoming

a positive crossmatch in living-donor kidney transplantation. *Am J Transplant*, 3(8), 1017-23 (2003)
DOI: 10.1034/j.1600-6143.2003.00180.x

56. Montgomery, R A, A A Zachary, L C Racusen, M S Leffell, K E King, J Burdick, W R Maley and L E Ratner: Plasmapheresis and intravenous immune globulin provides effective rescue therapy for refractory humoral rejection and allows kidneys to be successfully transplanted into cross-match-positive recipients. *Transplantation*, 70(6), 887-95 (2000)
DOI: 10.1097/00007890-200009270-00006

57. Schweitzer, E J, J S Wilson, M Fernandez-Vina, M Fox, M Gutierrez, A Wiland, J Hunter, A Farney, B Philosophe, J Colonna, B E Jarrell and S T Bartlett: A high panel-reactive antibody rescue protocol for cross-match-positive live donor kidney transplants. *Transplantation*, 70(10), 1531-6 (2000)
DOI: 10.1097/00007890-200011270-00023

58. Montgomery, R A, J E Locke, K E King, D L Segev, D S Warren, E S Kraus, M Cooper, C E Simpkins, A L Singer, Z A Stewart, J K Melancon, L Ratner, A A Zachary and M Haas: ABO incompatible renal transplantation: a paradigm ready for broad implementation. *Transplantation*, 87(8), 1246-55 (2009)
DOI: 10.1097/TP.0b013e31819f2024

59. Jordan, S C, D Tyan, L Czer and M Toyoda: Immunomodulatory actions of intravenous immunoglobulin (IVIG): potential applications in solid organ transplant recipients. *Pediatr Transplant*, 2(2), 92-105 (1998)

60. Yu, Z and V A Lennon: Mechanism of intravenous immune globulin therapy in antibody-mediated autoimmune diseases. *N Engl J Med*, 340(3), 227-8 (1999)
DOI: 10.1056/NEJM199901213400311

61. Everly, M J, J J Everly, B Susskind, P Brailey, L J Arend, R R Alloway, P Roy-Chaudhury, A Govil, G Mogilishetty, A H Rike, M Cardi, G Wadih, A Tevar and E S Woodle: Bortezomib provides effective therapy for antibody- and cell-mediated acute rejection. *Transplantation*, 86(12), 1754-61 (2008)
DOI: 10.1097/TP.0b013e318190af83

62. Walsh, R C, J J Everly, P Brailey, A H Rike, L J Arend, G Mogilishetty, A Govil, P Roy-Chaudhury, R R Alloway and E S Woodle: Proteasome inhibitor-based primary therapy for antibody-mediated renal allograft rejection. *Transplantation*, 89(3), 277-84 (2010)
DOI: 10.1097/TP.0b013e3181c6ff8d

63. Stegall, M D, T Diwan, S Raghavaiah, L D Cornell, J Burns, P G Dean, F G Cosio, M J Gandhi, W Kremers and J M Gloor: Terminal complement inhibition decreases antibody-mediated rejection in sensitized renal transplant recipients. *Am J Transplant*, 11(11), 2405-13 (2011)
DOI: 10.1111/j.1600-6143.2011.03757.x

64. Bray, R A and H M Gebel: Strategies for human leukocyte antigen antibody detection. *Curr Opin Organ Transplant*, 14(4), 392-7 (2009)
DOI: 10.1097/MOT.0b013e32832d31c7

65. Archdeacon, P, M Chan, C Neuland, E Velidedeoglu, J Meyer, L Tracy, M Cavaille-Coll, S Bala, A Hernandez and R Albrecht: Summary of FDA antibody-mediated rejection workshop. *Am J Transplant*, 11(5), 896-906 (2011)
DOI: 10.1111/j.1600-6143.2011.03525.x

66. Meier-Kriesche, H U, J D Schold, T R Srinivas and B Kaplan: Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. *Am J Transplant*, 4(3), 378-83 (2004)
DOI: 10.1111/j.1600-6143.2004.00332.x

67. Nankivell, B J, R J Borrows, C L Fung, P J O'Connell, R D Allen and J R Chapman: The natural history of chronic allograft nephropathy. *N Engl J Med*, 349(24), 2326-33 (2003)
DOI: 10.1056/NEJMoa020009

68. Paul, L C: Chronic allograft nephropathy: An update. *Kidney Int*, 56(3), 783-93 (1999)
DOI: 10.1046/j.1523-1755.1999.00611.x

69. Paul, L C: Chronic renal transplant loss. *Kidney Int*, 47(6), 1491-9 (1995)
DOI: 10.1038/ki.1995.211

70. Solez, K, R B Colvin, L C Racusen, B Sis, P F Halloran, P E Birk, P M Campbell, M Cascalho, A B Collins, A J Demetris, C B Drachenberg, I W Gibson, P C Grimm, M Haas, E Lerut, H Liapis, R B Mannon, P B Marcus, M Mengel, M J Mihatsch, B J Nankivell, V Nickeleit, J C Papadimitriou, J L Platt, P Randhawa, I Roberts, L Salinas-Madriga, D R Salomon, D Seron, M Sheaff and J J Weening: Banff '05 Meeting Report: differential diagnosis of chronic allograft injury and elimination of chronic allograft nephropathy ('CAN'). *Am J Transplant*, 7(3), 518-26 (2007)

DOI: 10.1111/j.1600-6143.2006.01688.x

71. Nankivell, B J and J R Chapman: Chronic allograft nephropathy: current concepts and future directions. *Transplantation*, 81(5), 643-54 (2006)
DOI: 10.1097/01.tp.0000190423.82154.01

72. Almond, P S, A Matas, K Gillingham, D L Dunn, W D Payne, P Gores, R Gruessner and J S Najarian: Risk factors for chronic rejection in renal allograft recipients. *Transplantation*, 55(4), 752-6; discussion 756-7 (1993)
DOI: 10.1097/00007890-199304000-00013

73. Massy, Z A, C Guijarro, M R Wiederkehr, J Z Ma and B L Kasiske: Chronic renal allograft rejection: immunologic and nonimmunologic risk factors. *Kidney Int*, 49(2), 518-24 (1996)
DOI: 10.1038/ki.1996.74

74. Kasiske, B L, R S Kalil, H S Lee and K V Rao: Histopathologic findings associated with a chronic, progressive decline in renal allograft function. *Kidney Int*, 40(3), 514-24 (1991)
DOI: 10.1038/ki.1991.240

75. Matas, A J, K J Gillingham, W D Payne and J S Najarian: The impact of an acute rejection episode on long-term renal allograft survival (t1/2). *Transplantation*, 57(6), 857-9 (1994)
DOI: 10.1097/00007890-199403270-00015

76. Chapman, J R: Longitudinal analysis of chronic allograft nephropathy: clinicopathologic correlations. *Kidney Int Suppl*(99), S108-12 (2005)
DOI: 10.1111/j.1523-1755.2005.09920.x

77. Nankivell, B J, R J Borrows, C L Fung, P J O'Connell, J R Chapman and R D Allen: Calcineurin inhibitor nephrotoxicity: longitudinal assessment by protocol histology. *Transplantation*, 78(4), 557-65 (2004)
DOI: 10.1097/01.TP.0000128636.70499.6E

78. Solez, K, F Vincenti and R S Filo: Histopathologic findings from 2-year protocol biopsies from a U.S. multicenter kidney transplant trial comparing tarolimus versus cyclosporine: a report of the FK506 Kidney Transplant Study Group. *Transplantation*, 66(12), 1736-40 (1998)
DOI: 10.1097/00007890-199812270-00029

79. Racusen, L C, K Solez, R B Colvin, S M Bonsib, M C Castro, T Cavallo, B P Croker, A J Demetris, C B Drachenberg, A B Fogo, P Furness, L W Gaber, I W Gibson, D Glotz, J C Goldberg, J Grande, P F Halloran, H E Hansen, B Hartley, P J Hayry, C M Hill, E O Hoffman, L G Hunsicker, A S Lindblad, Y Yamaguchi and et al.: The Banff 97 working classification of renal allograft pathology. *Kidney Int*, 55(2), 713-23 (1999)
DOI: 10.1046/j.1523-1755.1999.00299.x

80. Ojo, A O, P J Held, F K Port, R A Wolfe, A B Leichtman, E W Young, J Arndorfer, L Christensen and R M Merion: Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med*, 349(10), 931-40 (2003)
DOI: 10.1056/NEJMoa021744

81. Schwarz, A, H Haller, R Schmitt, M Schiffer, C Koenecke, C Strassburg, F Lehner, J Gottlieb, C Bara, J U Becker and V Broecker: Biopsy-diagnosed renal disease in patients after transplantation of other organs and tissues. *Am J Transplant*, 10(9), 2017-25 (2010)
DOI: 10.1111/j.1600-6143.2010.03224.x

82. Gallagher, M, M Jardine, V Perkovic, A Cass, S McDonald, J Petrie and J Eris: Cyclosporine withdrawal improves long-term graft survival in renal transplantation. *Transplantation*, 87(12), 1877-83 (2009)
DOI: 10.1097/TP.0b013e3181a76823

83. Sollinger, H W: Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. U.S. Renal Transplant Mycophenolate Mofetil Study Group. *Transplantation*, 60(3), 225-32 (1995)
DOI: 10.1097/00007890-199508000-00003

84. Naesens, M, E Lerut, B V Damme, Y Vanrenterghem and D R Kuypers: Tacrolimus exposure and evolution of renal allograft histology in the first year after transplantation. *Am J Transplant*, 7(9), 2114-23 (2007)
DOI: 10.1111/j.1600-6143.2007.01892.x

85. Murphy, G J, J R Waller, R S Sandford, P N Furness and M L Nicholson: Randomized clinical trial of the effect of microemulsion cyclosporin and tacrolimus on renal allograft fibrosis. *Br J Surg*, 90(6), 680-6 (2003)
DOI: 10.1002/bjs.4134

86. Irish, W, B Sherrill, D C Brennan, J Lowell and M Schnitzler: Three-year posttransplant graft survival in renal-transplant patients with graft function at 6 months receiving tacrolimus or cyclosporine microemulsion within a

triple-drug regimen. *Transplantation*, 76(12), 1686-90 (2003)
DOI: 10.1097/01.TP.0000090865.20886.B7

87. Meier-Kriesche, H U, J D Schold, T R Srinivas, R J Howard, S Fujita and B Kaplan: Sirolimus in combination with tacrolimus is associated with worse renal allograft survival compared to mycophenolate mofetil combined with tacrolimus. *Am J Transplant*, 5(9), 2273-80 (2005)
DOI: 10.1111/j.1600-6143.2005.01019.x

88. Kahan, B D: Efficacy of sirolimus compared with azathioprine for reduction of acute renal allograft rejection: a randomised multicentre study. The Rapamune US Study Group. *Lancet*, 356(9225), 194-202 (2000)
DOI: 10.1016/S0140-6736(00)02480-6

89. Halloran, P F: Sirolimus and cyclosporin for renal transplantation. *Lancet*, 356(9225), 179-80 (2000)
DOI: 10.1016/S0140-6736(00)02473-9

90. Ciancio, G, G W Burke, J J Gaynor, P Ruiz, D Roth, W Kupin, A Rosen and J Miller: A randomized long-term trial of tacrolimus/sirolimus versus tacrolimums/ mycophenolate versus cyclosporine/sirolimus in renal transplantation: three-year analysis. *Transplantation*, 81(6), 845-52 (2006)
DOI: 10.1097/01.tp.0000203894.53714.27

91. Lewis, E J, L G Hunsicker, R P Bain and R D Rohde: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med*, 329(20), 1456-62 (1993)
DOI: 10.1056/NEJM199311113292004

92. Jafar, T H, C H Schmid, M Landa, I Giatras, R Toto, G Remuzzi, G Maschio, B M Brenner, A Kamper, P Zucchelli, G Becker, A Himmelmann, K Bannister, P Landais, S Shahinfar, P E de Jong, D de Zeeuw, J Lau and A S Levey: Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. *Ann Intern Med*, 135(2), 73-87 (2001)
DOI: 10.7326/0003-4819-135-2-200107170-00007

93. Hiremath, S, D Fergusson, S Doucette, A V Mulay and G A Knoll: Renin angiotensin system blockade in kidney transplantation: a systematic review of the evidence. *Am J Transplant*, 7(10), 2350-60 (2007)
DOI: 10.1111/j.1600-6143.2007.01928.x

94. Akalin, E, S Dikman, B Murphy, J S Bromberg and W W Hancock: Glomerular infiltration by CXCR3+ ICOS+ activated T cells in chronic allograft nephropathy with transplant glomerulopathy. *Am J Transplant*, 3(9), 1116-20 (2003)
DOI: 10.1034/j.1600-6143.2003.00151.x

95. Ivanyi, B: Transplant capillaropathy and transplant glomerulopathy: ultrastructural markers of chronic renal allograft rejection. *Nephrol Dial Transplant*, 18(4), 655-60 (2003)
DOI: 10.1093/ndt/gfg139

96. Gloor, J M, S Sethi, M D Stegall, W D Park, S B Moore, S DeGoey, M D Griffin, T S Larson and F G Cosio: Transplant glomerulopathy: subclinical incidence and association with alloantibody. *Am J Transplant*, 7(9), 2124-32 (2007)
DOI: 10.1111/j.1600-6143.2007.01895.x

97. Akalin, E, R Dinavahi, S Dikman, G de Boccardo, R Friedlander, B Schroppel, V Sehgal, J S Bromberg, P Heeger and B Murphy: Transplant glomerulopathy may occur in the absence of donor-specific antibody and C4d staining. *Clin J Am Soc Nephrol*, 2(6), 1261-7 (2007)
DOI: 10.2215/CJN.02420607

98. Joosten, S A, Y W Sijpkens, V van Ham, L A Trouw, J van der Vlag, B van den Heuvel, C van Kooten and L C Paul: Antibody response against the glomerular basement membrane protein agrin in patients with transplant glomerulopathy. *Am J Transplant*, 5(2), 383-93 (2005)
DOI: 10.1111/j.1600-6143.2005.00690.x

99. Dinavahi, R, A George, A Tretin, E Akalin, S Ames, J S Bromberg, G Deboccardo, N Dipaola, S M Lerner, A Mehrotra, B T Murphy, T Nadasdy, E Paz-Artal, D R Salomon, B Schroppel, V Sehgal, R Sachidanandam and P S Heeger: Antibodies reactive to non-HLA antigens in transplant glomerulopathy. *J Am Soc Nephrol*, 22(6), 1168-78 (2011)
DOI: 10.1681/ASN.2010111183

100. Cosio, F G, J M Gloor, S Sethi and M D Stegall: Transplant glomerulopathy. *Am J Transplant*, 8(3), 492-6 (2008)
DOI: 10.1111/j.1600-6143.2007.02104.x

101. Kim, M G, Y J Kim, H Y Kwon, H C Park, T Y

Koo, J C Jeong, H J Jeon, M Han, C Ahn and J Yang: Outcomes of combination therapy for chronic antibody-mediated rejection in renal transplantation. *Nephrology (Carlton)*, 18(12), 820-6 (2013)
DOI: 10.1111/nep.12157

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Send correspondence to: Rajani Dinavahi, One Amgen Center Dr, Bldg 38, Mail Stop 38-3C, Thousand Oaks, CA 91320, Tel: 805-447-2231, E-mail: rajanid@amgen.com