Chronic Allograft Nephropathy – Immunologic and Nonimmunologic factors

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Abstract:
Chronic Allograft Nephropathy (CAN) is one of the most common cause of kidney transplant loss. CAN may be caused by immunologic as well as nonimmunologic factors which may interfere and increase response. Immunologic factors include acute rejection, degree of HLA mismatch, inadequate immunosuppression. Nonimmunologic factors contain delayed graft function, ischemia – reperfusion injury, nephrotoxicity of calcineurin inhibitors, hyperfiltration, hypertension and hyperlipidemia. The histopatological description of CAN may indicate two phases of injury. An initial phase by one year include tubulointerstitial infiltration in the late phase of CAN arteriolar hyalinosis and glomerulosclerosis were revealed. Modification of the immunosuppressive treatment with reduction or withdrawal of calcineurin inhibitors may prevent graft loss, while addition of nonnephrotoxic agents such as mycophenolate mofetil or sirolimus should be considered by the risk of acute rejection. Additionally effective management by hypertension and hyperlipidemia is essential.

Key words: Kidney Transplant; Chronic Allograft Nephropathy; Immunologic and Nonimmunologic Factors

Introduction

Chronic Allograft Nephropathy (CAN) is the term to the progressive loss of allograft function that occurs months or years after transplantation. CAN is liable for 27% to 40 % of all graft failures between 1 and 3 years after renal transplantation [1]. CAN is more useful term than the often used „chronic rejection" which concerns only immunologic response. CAN is caused not only by immunologic but also nonimmunologic factors related to the kidney donor and recipient. Alloantigen-dependent mechanisms include HLA matching, subclinical and acute rejection by inadequate immunosupresion. On the other hand there are alloantigen-independent processes (donor brain death, delayed graft function-DGF, recipient and donor characteristics, ischemia reperfusion injury, drug-induced nephrotoxicity, hypertension, hyperlipidemia, bacterial and virus infections) which have been shown to influence deterioration of graft function. Some of these processes induced the immune system stimulating production of cytokines and growth factors. Clinical manifestations present deterioration in kidney function (evidenced slow, progressive increase in serum creatinine and decline in GFR), proteinuria (usually 1-2 g/day), and arterial hypertention. Renal histopathological changes include interstitial fibrosis and tubular atrophy, accompanied by glomerulosclerosis, often with concentric intimal thickening of arteries and arterioles [2].

Significance of chronic allograft nephropathy in kidney transplantation

CAN, besides death of the recipient with functioning graft, is the most common cause of kidney transplant loss. Krieger et al. respectively examined 2,140 transplants [3]. In the analysis there were 522 graft losses. Biopsy-proven CAN defined by the Banff criteria [2] along with the clinical features was the primary endpoint. Patients and graft survival were the secondary endpoints. The incidence of graft loss because of CAN was 32% and death with functioning graft concerned 34% of patients. In another study Matas et al. reported that CAN was liable for graft loss before 1 year in 12% of patients between 5 and 10 years in 35% and at 10 years in 33% [4]. Transplant function within the first year of transplantation has been noticed as an important factor of graft survival [5-9].

Hariharan et al. showed the influence of post-transplant renal function on long-term transplant survival [10]. In this study 105,742 renal transplant were included. Patients were divided in six group according to their one year posttransplant serum creatinine. The Kaplan-Meier method was used to estimate long-term graft survival. This study demonstrated that one year creatinine value is a strong predictor of transplant survival. Creatinine over 1.5 mg/dl one year after transplantation and Δ creatinine ≥ 0,3 mg/dl were associated with a deterioration in long-term renal graft survival. A decline in graft half-life was connected with progressive increases in one year creatinine levels. For instance projected median graft half-life for cadaveric kidney in years according to 1 year post-transplant creatinine value: with creatinine <1.0mg/dl is 14.0years; between 1.1 and 1.5 mg/dl – 13.2 years; over 1.6 to 2.0mg/dl – 9.4years.

CAN is a factor which increases the probability of graft loss. In death-censored graft survival studies CAN is the first cause of late graft deterioration and failure. A total of 50% of recipients with CAN lose graft function within 5 years of transplantation. The recipients who return to dialysis beyond 2 years (50-80%) are touched by CAN.

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Chronic allograft nephropathy – multifactor pathogenesis, histological injuries

CAN is caused by immunologic and nonimmunologic factors. Immunologic factors include acute rejection, degree of HLA mismatch, inadequate immunosuppression. Nonimmunologic factors contain delayed graft function, ischemia – reperfusion injury, nephrotoxicity of calcineurin inhibitors (CNI), hyperfiltration, hypertension and hyperlipidemia. These two mechanisms of activity can interfere and increase response what deteriorates graft failure.

Nankivell et al. presented the landmark prospective study which included 961 kidney allograft biopses performed in 120 recipients with type 1 diabetes (taken from time of grafting to 10 years thereafter) [11]. This first longitudinal description of CAN indicated two distinctive phases of injury. An initial phase predicted mild disease by year one and was present in 94.2% of recipients. The injuries were described as tubulointerstitial damage from ischemic injury, severe rejection and subclinical rejection. The late phase of CAN (beyond one year) revealed arteriolar hyalinosis, glomerulosclerosis and additional tubulointerstitial damage. Calcineurin-inhibitor nephrotoxicity was almost general in transplants at 10 years. There is the paradox that a renal transplant which is protected from immunologic injury by calcineurin inhibitors is damaged as a result of nephrotoxicity caused by these same drugs. This renal transplant histology analysis suggests that CNI minimization and withdrawal protocols are a way to improving transplant outcomes.

In the authors centre the impact of ischemia-reperfusion injury and acute rejection on the long-term renal transplant function was analysed. The total of 248 kidney transplant recipients were included. Independent risk factors for the increase serum creatinine above 1.5 mg/dl after the first post transplantation year (multivariate logistic regression analysis) were the occurrence of delayed graft function (OR 2.9) and the appearance of acute rejection (OR 2.5). If the DGF is not connected with acute rejection the effect is impermanent. However, after 24 months the independent predictor of impaired renal transplant function was exclusively the appearance of acute rejection (OR 2.2). The high-producing TGF-β1 genotype of the recipients correlated with the delayed graft function occurrence and with the acute rejection appearance.

Nonimmune determinants of the recipient and kidney allograft survival

The approach to hypertension, hyperlipidemia, proteinuria, new onset diabetes and anemia should be in the renal transplant recipients treated equally meticulous as in the patients with native kidney disease.

In the largest trial of fluvastatin (Assessment of Lescol in Renal Transplantation -ALERT) performed in transplant recipients (2,102 pts included) the effect of cholesterol reduction was investigated. Although there was a 35% reduction in cardiac deaths and nonfatal myocardial infarction, fluvastatin did not reduce rates of coronary intervention procedures or mortality. Fluvastatin treatment also had no effect on graft loss or doubling of serum creatinine [12].

The recent analysis of ALERT trial study has shown that serum creatinine, proteinuria, and pulse pressure at baseline (mean time since last transplantation 5.5 years) were independent risk factors renal endpoints [13]. Diabetes mellitus, smoking, and signs of LVH were also independent risk factors if patient death was included in the composite endpoints. The use of renoprotective regimens (ACE inhibitor or AIIRA received 50% of patients), effective treatment of hypertension, reduction of proteinuria, and cessation of smoking should form a key treatment approach for improving cardiac and renal outcomes.

Immunological monitoring – way to individualization of immunosuppressive regimen

There are promissing assays which may guide to the implementation of calcineurin inhibitors withdrawal or minimization protocols:

- Measuring T-cell alloreactivity: mixed lymphocyte reaction (MLR); cell-mediated lymphocytotoxicity (CML); limiting dilution assay; cytokine analyses (ELISA, ELISPOT, flow cytometry)
- Humoral immune response: alloantibody monitoring
- Profiling of immune cells: lymphocyte activation markers by flow cytometry blood, urine, graft infiltrating cells.
- Profiling circulating DC subsets
- Immune gene polymorphisms

The ELISPOT assay for leukocytes producing interferon-gamma in response to stimulator cells from donor independently predicts renal function in kidney transplant recipients [14]. Patients with low mean frequencies of interferon-producing cells in the early post-transplant period (< 10 per 300 000 PBLs) exhibited excellent renal function at 6 and 12 months after the transplantation. Increased levels of interferon-gamma may be used as a substitute for CAN.

The combined analysis of alloimmunity (IFN-γ ELISPOT assay, new anti-HLA antibodies) were performed by Poggio et al. in transplant recipients [15]. A total of 12 (60%) of 20 of those with abnormal renal function were observed, but only 4 (16%) of 25 control subjects with good graft function. No alloimmune response were detected in 84% of control subjects with good graft function, 40% of patients with abnormal renal function, and 22% of those with biopsy confirmed CAN.

Evaluation of immune reactivity in renal transplant recipients

Patients without detectable peripheral immune reactivity but with slowly deteriorating renal function and minimal inflammation in an allograft biopsy, may be the best candidates for calcineurin inhibitor withdrawal. In contrast, recipients with persistently detectable immune reactivity, worsening renal

function may benefit from intensification of immunosuppressive therapy.

Strategies to prevent chronic allograft nephropathy

There may be different ways for the improvement of renal function after transplantation. Immune strategies to combat CAN progression include:

- Calcineurin minimization or withdrawal in conjunction with mycophenolate mofetil
- Calcineurin minimization or withdrawal in conjunction with sirolimus
- New emerging option: everolimus in combination with reduced dose calcineurin inhibitors.

Additionally treatment of acute rejection, management of DGF or better control of hypertension and hyperlipidemia should be appropriately managed.

Calcineurin-inhibitor reduction with or without MMF treatment

An important role in long term graft survival is the tacrolimus and cyclosporine nephrotoxicity. Individualization of calcineurin inhibitors treatment is a way to improve graft function. On the other side calcineurin-inhibitor avoidance even with antibody induction, mycophenolate mofetil (MMF), and corticosteroids can not appropriately prevent acute rejection. Protocols containing either daclizumab or rabbit antithymocyte globulin with mycophenolate mofetil and corticosteroids were associated with a high incidence of acute rejection (24 to 53%) and should be avoided even in low-immunologic risk patients.

Protocols including sirolimus, mycophenolate mofetil and corticosteroids with antibody induction (basiliximab) were related with the lower incidence of antibody rejection (AR) in the sirolimus-MMF group (6%) than the cyclosporine-MMF group (17%). Sirolimus treated patients had significantly higher calculated GFR but they also exhibited higher incidences of hyperlipidemia and bone marrow toxicities.

The reduction of cyclosporine with the addition of azathioprine (AZA) or MMF has effected in better graft function in patients with CAN [16-19]

The usefulness of MMF as replacement for CsA in patients with chronic allograft nephropathy was shown in Dudley et al. study [20].

CsA-treated patients with progressive chronic allograft nephropathy (n = 122) were randomized to have either CsA discontinued with the concomittant addition of MMF or to continue treatment with CsA. Response was defined as the stabilization or reduction of serum creatinine over the 6-month period. The response rate was: 60% in MMF group vs. 26% in CsA group ($p<0.0008$). Patients in MMF group also experienced a significant decrease in total cholesterol. This analysis has demonstrated that complete withdrawal of CsA with addition of MMF followed by results in a significant improvement in renal function without the risk of acute rejection.

Late calcineurin inhibitor withdrawal in patients with CAN has been shown as a treatment strategy to minimize possibility of graft failure [21]. Weir et al. in their study of 105 renal graft recipients with impaired renal function reduced or discontinued in these patients the dose of CsA, or tacrolimus (TAC) with either the addition of, or continuation of MMF. The results presented 24 graft failures in the reduced CsA group, 9 graft failures in the reduced TAC group, and 1 graft lost in the calcineurin inhibitor withdrawal group.

The Afzali et al. analysis of 89 patients with CAN, who received MMF with starting dose 500-1.000 mg/day (increased by 50% over next few weeks) and a phased reduction in calcineurin inhibitors (CNI) (to achieve CsA levels of 25-50 ng/ml, or TAC levels of approximately 5) by 3 months after starting MMF showed that low-dose MMF was well tolerated and resulted in prolonged graft survival [22].

Sirolimus in the management of CAN

Conversion to sirolimus (SRL) with sharp withdrawal of calcineurin inhibitor was evaluated among patients with progressive chronic renal allograft dysfunction. SRL target trough level was 8-10 ng/ml. Response to conversion included amelioration of kidney dysfunction in 36% of patients and stabilization in 21%, whereas 43% experienced continued deterioration. Recipients with improvement or stabilization were converted at a significantly lower serum creatinine (2.6 vs. 3.3 mg/dl) [23].

The reduction of cyclosporine dose by 40% with sirolimus addition has not shown to be more effective against CAN than without sirolimus [24]. A total of 31 patients with CAN received 40% cyclosporine reduced dose with or without rapamycin. Rapamycin (2 mg/day) added after cyclosporine reduction did not improve GFR.

Conclusions

The pathogenesis of CAN is complicated and multifactorial. Cautious modification of the immunosuppressive regimen to reduce or eliminate exposure to calcineurin inhibitors may help to prevent graft fibrosis, including of non-nephrotoxic agents such as mycophenolate or sirolimus may be considered after carefully balancing the risk of acute rejection. In addition, effective management of comorbid diseases states such as hypertension and hyperlipidemia is essential.

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References

1. Cecka JM: The UNOS Scientific Renal Transplant Registry, in: Cecka JM, Terasaki PI (Eds): Clinical transplants 2000. Los Angeles, UCLA Immunogenetics Center 2001, p 1.
2. Racusen LC, Solez K, Colvin RB, et al.: The Banff 97 working classification of renal allograft pathology. Kidney Int 1999; 55: 713-723.
3. Krieger N, Becker B, Heisey D, et al.: Chronic allograft nephropathy uniformly affects Recipients of cadaveric, nonidentical living-related, and living-unrelated grafts. Transplantation 2003; 75: 1677-1682.
4. Matas AJ. Chronic rejection in renal transplant recipients: Risk factors and correlates. Clin Transplant 1994; 8: 332.
5. Cecka JM: The UNOS Scientific Renal Transplant Registry, in: Cecka JM, Terasaki PI (Eds): Clinical transplants 1998. Los Angeles, UCLA Tissue Typing Laboratory, pp 116.
6. Nicol D, MacDonald AS, Belitsky P: Early prediction of renal allograft loss beyond one year. Transplant Int 1993; 6: 153157.
7. Giral M, Taddei C, Nguyen JM, et al: Single center analysis of 468 first cadaveric kidney allograft with uniform ATG-CsA sequential therapy, in Clinical Transplants 1996, edited by MJ Cecka, Terasaki PI, Los Angeles, UCLA Tissue Typing Laboratory, pp 257264.
8. Humar A, Kerr S, Gillingham KJ, Matas AJ: Features of acute rejection that increase risk for chronic rejection. Transplantation 1999; 68: 12001203.
9. Ishikawa A, Flechner SM, Goldfarb DA, et al.: Significance of serum creatinine pattern and area under the creatinine versus time curve during the first acute renal transplant rejection. Transplant Proc 2000; 32: 781783.
10. Hariharan S., McBride MA, Cerikh WD, et al.: Post-transplant renal function in the first year predicts long-term kidney transplant survival Kidney International 2002; 62: 311-318.
11. Nankivell BJ, Borrows RJ, Fung CL: The natural history of chronic allograft nephropathy. N Engl J Med. 2003; 349: 2326-2333.
12. Holdaas H, Fellstrom B, Jardine AG, et al.: Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. Assessment of Lescol in Renal Transplantation (ALERT) study Lancet 2003; 361: 2024-2031.
13. Fellstrom B, Holdaas H , Jardine AG, et al.: Risk Factors for Reaching Renal Endpoints in the Assessment of Lescol in Renal Transplantation (ALERT) Trial , Transplantation 2005; 79: 205.
14. Hricik DE, Rodriguez V, Riley J, et al.: Enzyme linked immunosorbent spot (ELISPOT) assay for interferon-gamma independently predicts renal function in kidney transplant recipients. Am J Transplant. 2003; 3: 878-884.
15. Poggio ED, Clemente M, Riley J, et al.: Alloreactivity in renal transplant recipients with and without chronic allograft nephropathy. J Am Soc Nephrol 2004; 5: 1952-1960.
16. Hollander AA, Van Saase JL, Kootte AM, et al.: Beneficial effects of conversion from cyclosporin to azathioprine after kidney transplantation. Lancet 1995; 345: 610.
17. Mourad G, Vela C, Ribstein J, Mimran A: Long-term improvement in renal function after cyclosporine dose reduction in renal transplant recipients with histologically proven chronic cyclosporine nephrotoxicity. Transplantation 1998; 65: 661.
18. Weir MR, Anderson L, Fink JC, et al.: A novel approach to the treatment of chronic allograft nephropathy. Transplantation 1997; 64: 1706.
19. Hueso M, Bover J, Seron D, et al.: Low-dose cyclosporine and mycophenolate mofetil in renal allograft recipients with suboptimal renal function. Transplantation 1998; 66: 1727.
20. Dudley Ch, Pohanka E, Riad H. et al. : MMF substitution for CsA in renal transplant recipients with chronic progressive allograft dysfunction: the "creeping creatinine" study. Transplantation 2005; 79: 466.
21. Weir MR, Blahut S, Drachenburg C, et al.: Late Calcineurin Inhibitor Withdrawal as a Strategy to Prevent Graft Loss in Patients with Suboptimal Kidney Transplant Function. Am J Nephrol 2004; 24: 379-386.
22. Afzali B, Shah S, Chodwdhury P, et al.: Low- dose MMF permits phased reduction in CNIs in chronic allograft nephropathy. Transplantation 2005; 79: 304.
23. Citterlo F, Scata MC, Violi P, et al.: Rapid conversion to sirolimus for chronic progressive deterioration of the renal function in kidney allograft recipients. Transplant Proc 2003; 35: 1292-1294.
24. Saunders RN, Bicknell GR, Nicholson ML: The impact of cyclosporine dose reduction with or without the addition of rapamycin on functional, molecular, and histological markers of chronic allograft nephropathy. Transplantation 2003; 75: 772.