CHAPTER 5

Summary and Recommendations

1. IMMUNOLOGIC INTERVENTION TO PREVENT CAN.

Prevention

- We treat patients with triple maintenance immunosuppressive therapy, aiming for a regimen that includes a calcineurin inhibitor (such as cyclosporine or tacrolimus,prdnisone, and an antimetabolite. Despite the possible increased risk of chronic allograft nephropathy due to calcineurin-inhibitor therapy with this approach, the immunosuppressive benefits of this regimen outweigh its possible adverse effects.
- Calcineurin free regimens are promising regimens in low to moderate risk candidates for kidney transplantation.
- There are preventive measures related to immunosuppressive issues and CAN. These include optimizing HLA matching, reducing acute rejection episodes and ischemic injury (which increases proinflammatory cytokines and others), and avoiding sensitization.

Treatment

Among those with chronic allograft nephropathy receiving cyclosporine (particularly those with histologic lesions most consistent with cyclosporine injury eg, arteriolar hyalinosis), some evidence suggests that a decrease in or withdrawal of cyclosporine therapy may be effective. Thus, we either decrease the cyclosporine dose or possibly switch from cyclosporine to tacrolimus (as there is evidence of less induction of TGF-beta and fibrosis with tacrolimus).

Among those with low calcineurin inhibitor levels and a GFR higher than 50 mL/min, consideration is given to substituting sirolimus for the calcineurin inhibitor. Caution must be exercised in this setting as an ongoing clinical trial was terminated because of excess pneumonia and death among those with GFRs less than 40 mL/min in whom this substitution was performed. In addition, we do not use sirolimus in patients with proteinuria of greater than one gram/day, unless there are other overriding concerns. The substitution of mycophenolate mofetil, if not being administered, for azathioprine may also ameliorate progressive renal dysfunction as shown in some studies (***Agroudy et al.,2006-Creeping creatinine study.....)***

Although the significance of positive C4d staining or positive donor specific antibody in the chronic setting is unclear, these findings may represent a chronic process of antibody-mediated rejection that might be forestalled through augmentation of the immunosuppressive regimen. We convert to or augment the dose of tacrolimus and mycophenolate mofetil in those with chronic allograft nephropathy and positive C4d staining, with or without the presence of donor specific antibodies. In the setting of positive C4d staining alone without histologic evidence of chronic nephropathy in the late transplant period, we have generally followed the same protocol. We repeat donor specific antibody titers after making changes in the immunosuppressive regimen.

Future plans

Future of kidney transplantation in the next era is toward minimization of immunosupression to avoid its toxic effects on both patient and graft(***Kirk A et al,2003***),this is may be applied through many approaches targeting to induce tolerance.these approaches can be summarized as follows:

1) Chemokine Blockade

The process of allograft rejection requires recruitment of leukocytes into lymphoid compartments and their emigration into the allograft. The steps of leukocyte recruitment are dependent on local concentrations of chemokines, a process that has become the subject of intensive scientific interest. The chemokine receptor CXCR3 has been linked to the development of acute rejection and patients with a deletion of the CCR5 chemokine receptor gene may have prolonged graft survival. Strategies to inhibit chemokine activity may have important applications in clinical transplantation.(***Li y et al,1999).***

2) Immune Modulation

Immune modulation is term used to describe attempts to modify the immune response in a nonspecific fashion in order to facilitate allograft acceptance without impairing effector cells or mechanisms. Several techniques fall within this category.Infusion of donor-specific bone marrow, in combination with short-term nonspecific immunosuppression, has produced long-term graft survival in the absence of immunosuppressive therapy in

experimental and clinical organ allografts. The donor bone marrow provides an as yet unidentified signal for tolerance. Blood transfusions are known to exert beneficial effects on animal and human allograft survival through a variety of potential mechanisms. The tolerogenic effect of bone marrow and blood may also be a result of the development of a state of microchimerism . A randomized trial of perioperative donor-specific blood transfusions in live donor transplants showed no practical benefit.

3) New biologic agents

Alemtuzumab (Campath 1H) is an anti-CD52 monoclonal antibody approved for use in chronic lymphocytic leukemia that is a potentially valuable depletional agent in clinical transplantation. When used at the time of transplant as induction therapy, alemtuzumab induces a profound, rapid and effective depletion of peripheral and central lymphoid cells that may take months to return to pretransplant levels. Used as a single agent it does not induce tolerance and episodes of acute rejection can occur even in the absence of T cells. Its use facilitates minimization of maintenance immunosuppressive protocols and steroid sparing with monotherapy using sirolimus or low-dose calcineurin inhibitor***(Knechtle SJ et al,2003)***

II. Non immunologic intervention to prevent CAN.

A. Management of dyslipidemia

I. Very high triglycerides

Among patients with triglyceride levels >500 mg/dL, we first attempt lifestyle modifications in an attempt to decrease levels to less than 500 mg/dL. If such lifestyle changes are inadequate after three months, we try monotherapy with either ezetimibe (10 mg daily) or nicotinic acid (beginning with 250 mg per day and advancing slowly to 2 grams per day). We usually start with ezetimibe unless insurance or costs necessitate the use of nicotinic acid. As previously mentioned, we avoid fibrates, such as gemfibrozil, given the potential toxicity associated with these agents. In addition, the 2004 K/DOQI guidelines stated that ezetimibe should probably not be used in the transplant setting, until its safety was established.

II. Elevated LDL-cholesterol levels

Taken together, the available body of evidence shows a consistent benefit of statin therapy upon cardiovascular risk surrogates and possibly upon clinical cardiac events in kidney transplant patients. However, a major concern in the transplant recipient has been a relatively high incidence of a clinically significant myopathy in patients also treated with cyclosporine. Starting with a low statin dose substantially decreases the risk of muscle toxicity, and individual statins have different degrees of muscle toxicity.

Issues surrounding the choice of a particular statin in the transplant population therefore involve balancing the relative risk of adverse effects (including adverse drug interactions) with efficacy (particularly in terms of cardiovascular benefit)., the largest experience in the kidney transplant population is with fluvastatin in the ALERT study, which found a non-significant trend with active therapy towards a reduction in the primary composite outcome and no difference in side effects ***(Holdaas et al., 2003)***.

With respect to the general population, a number of statins have shown substantial benefit in terms of cardiovascular mortality, particularly atorvastatin. By comparison, there is a paucity of data concerning the efficacy of this agent in the kidney transplant population. Despite this, statin of choice is atorvastatin because of superior results compared to other statins in non-transplant recipients, increased potency compared with fluvastatin, and, in our experience, very few adverse events or drug interactions with cyclosporine, tacrolimus, and sirolimus.

Among patients with LDL $\geq$ 100 mg/dL, we use atorvastatin beginning at 10 mg/day,aiming for a goal LDL-cholesterol of less than 70 mg/dL for secondary prevention of coronary heart disease. To attain this level, we increase atorvastatin to a maximum dose of 80 mg/day or only to 40 mg/day in those also receiving cyclosporine or tacrolimus. If this dose fails to lower LDL-cholesterol levels adequately, we add ezetimibe as an additional agent. If myopathy or drug interactions occur, a trial of fluvastatin or parvastatin may be considered instead of

atorvastatin, because these alternative statins have little or no muscle toxicity and are not metabolized by CYP3A4.

Because of the side effects associated with atorvastatin, others prefer to initiate statin therapy with fluvastatin or pravastatin instead of atorvastatin. Due to the frequent side effects associated with fibrates and nicotinic acid, we use ezetimibe as either an additional agent when necessary or as our second choice when a statin is not tolerated ***(Abbud-Filho et al., 2007)***.,The 2004 K/DOQI guidelines, by comparison, stated that ezetimibe should probably not be used in the transplant setting, until its safety was established ***(Kasiske et al., 2004)***.

3. Elevated non HDL-cholestrol

As a part of metabolic syndrome,elevation of non HDL cholestol levels and triglycerides are linked with cardiovascular risk like pattern in general population(***Cui et al., 2001)***so this pattern ofdyslipidemia is managed by:

I. Atorvastatin 10 mg reaching maximum 80 mg/day or 40mg/day in patients recieving tacrolimus or cyclosporine.
II. If myopathy or drug interaction occurs,a trial of fluvastatinor parvastatin may be considered instead

B. Management of PTDM

Post-transplant diabetes mellitus occurs in roughly 25 percent of patients in the first three years after renal transplantation. Its development is associated with increased recipient age >40 to 45 years, obesity, African-American or Hispanic ancestry, HCV infection, and calcineurin inhibitor and corticosteroid use. Development of PTDM is associated with significant infectious and cardiovascular morbidity as well as increased mortality.

Management begins pretransplantation with screening for impaired glucose tolerance, PTDM risk assessment and counseling. Immunosuppression plans should consider an individual's risk for PTDM risk, which should be weighed against concerns for rejection. Post-transplantation, patients should undergo regular screening for PTDM development. Aggressive attention to other

cardiovascular risk factors may help reduce the increased mortality seen in patients with impaired glucose tolerance post-transplantation. Finally, adjustment in immunosuppressive therapy may improve glucose tolerance.

A stepwise approach is recommended for the management of PTDM, starting with non-pharmacologic therapy, followed by oral monotherapy, oral combination therapy, and then insulin as long as no metabolic decompensation occurred to require earlier insulin initiation.

- With oral therapy, we usually initiate oral therapy with glipizide at a dose of 5 mg per day and then advance to 10 mg twice per day as necessary to maintain the HbA1c level at less than 7 percent. If this is insufficient, we will add rosiglitazone, if necessary and as tolerated. In some patients, we begin oral therapy with rosiglitazone as our first agent. Beyond these doses, we usually find it necessary and safer to begin insulin therapy in place of oral therapy.

- We initiate insulin therapy if there has been metabolic decompensation, adverse side effects with oral therapy, or HbA1c levels that are consistently above 7 percent. In addition, many patients will require institution of insulin, especially those with fasting blood sugars above 200 mg/dL. We may use multiple agents and/or multiple-dose intensive insulin therapy or insulin-pump therapy.

C. Management of hypertension after kidney transplantation

- **K/DOQI guidelines for controlling blood pressure are applied**

  1. Target blood pressure in non proteinuric patients 130/80mmHg
  2. Target blood pressure in patient with significant proteinuria(0.5-1gram per day)is 125/75.

- **Types of applied antihypertensive drugs**

1. In patients taking a calcineurin-inhibitor

a) Reduce calcineurin-inhibitor as possible.

b) Then try CCB.

c) Then you can add ACEI or ARBS(but with caution as they may decrease GFR or increase serum potassium)

2. In patients not taking calcineurin-inhibitors.

a) Such patients should start immediately antihypertensive.

b) CCB,ACEI and betablockers,all may be effective.

c) Diuretics may be necessary in patients with graft dysfunction in whome volume expansion may be responsible for hypertension.

- **Patients with resistant hypertension.**

a) Such patients should renal angiography.

b) Check for urinary sediments to exclude recurrent disease.

D. Use of ACEI/ARBS

We initiate a trial of ACE inhibitor or ARB therapy in patients with chronic allograft nephropathy, particularly those with diabetes and/or proteinuria. Since the decline in glomerular filtration rate induced by an ACE inhibitor typically occurs within the first few days of therapy, the plasma creatinine and potassium concentrations should be remeasured two to five days after the institution of therapy. We also routinely measure hemoglobin levels, since ACE inhibitors can induce anemia.

III. INTERPLAY BETWEEN IMMUNOLOGIC AND NON IMMUNOLOGIC FACTORS.

Both factors are reflected on each other. for example,use of tacrolimus can make DM difficult to control and hence increase incidence of infections (one of causes of death with functioning graft).On the other side,serious infections may necessitates stoppage of immunosupression and consequently predispose to graft rejection and return to dialysis.see figure (6) which shows how both immunologic and non immunologic factors intract to induce chronic allograft nephropathy and also death with functioning graft.

So,judicious balance should be acted upon and we can summarize points of balance as follows:

1) Tailoring of immunosuppression,see table number (9).
2) Optimum intensification of immunnosupression during early period especially for risk groups (prior sensitization,children,etc.....) to avoid episodes of acute rejections that requires either pulse steroids or polyclonal antibodies(pulse steroid predispose PTDM and infections while polyclonal antibodies predispose infections especially viral and PTLD).
3) Limiting exposure to calcineurine inhibitors among stable patients.
4) Steroid tapering to 5mg/day by the end of first year among stable patients(low risk for rejection).also steroid free regimens should be applied to risky patients to develop PTDM or patients with DM difficult to control provided that these patients have no high risk for rejection also.
5) Pay a great attention to drug-drug interaction while prescribing drugs that interfere with metabolism of immunosuppressive drugs (decreasing their metabolism and enhancing toxicity or increasing their destruction and enhancing rejection).For example antituberculous eg.Rifampicin acts as an enzyme inducer through cytochrome p-450 decreasing the level of tacrolimus and the patient requires elevation of the FK dose with frequent monitoring of the level to avoid rejection.see table (10) that clarify possible drugs that interact with immunosuppressive drugs.

Table number 8: tailoring of immunosupression

Modified from Hand book of kidney transplantation-fourth addition-ninth chapter(long term post transplant management and complications byMeena Sahadevan and BertramL.Kasiske.

Risk factor or complication	**Agent to reduce or withdrawl**
Severe hyperlipidemia	Cyclosporine,steroid,Rapamycin
Severe hypertension	Cyclosporine ,steroids
Difficult to control DM	Tacrolimus,Steroids
Anaemia-neutropenia-thrombocytopenia	AZA,MMF,Rapamycin
Gout requiring alloprinol	Azathioprine

Table no (10):interaction between immunosuppressive drugs and others

Modified from handbook of kidney transplantation(fourth edition)chapter number 10(infections in kidney transplantation).

Intractin agent	Immunosup.drug	Interaction
Azithromycin	CsA, Sir	Increases CsA/Sir level
Erythromycin	CsA, Tac, Sir	Increases CsA/Tac/Sir level
Fluconazole, itraconazole, ketoconazole	CsA, Tac, Sir	Increases CsA/Tac/Sir level
Isoniazid	Sir	Increases Sir level
Pyrazinamide	CsA	Decreases CsA level
Rifampin, rifabutin	CsA, Tac, Sir	Decreases CsA/Tac/Sir level
Ciprofloxacin	CsA	Increases CsA level and nephrotoxicity
Norfloxacin	CsA	Increases CsA level and nephrotoxicity
Ofloxacin	CsA	Increases CsA level
Sulfamethoxazole and trimethoprim	CsA	Decreases CsA level, increases incidence of nephrotoxicity
Amphotericin B	CsA, Tac	Increases incidence of nephrotoxicity
verapamil,	CsA,TaC	Increase CsA,TaC level
diltiazem	CsA,TaC	Increase CsA,TaC level
Antiepileptics	CsA,TaC	Decrease CsA,TaC level