

## **A Critical Appraisal of the Possible Use of Induction Agents in Low Risk Kidney Transplant Recipients: A Nigerian Perspective**

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### **ABSTRACT**

Kidney transplant is now generally accepted as the treatment of choice for patients with end-stage renal disease. This is because of its association with improved survival and quality of life when compared with other forms of renal replacement therapy. Immunosuppression including induction has played a strong role over the years in improving the outcomes of renal transplant.

The main aim of transplant immunosuppression is renal allograft survival in the long term and the patient survival while at the same time reducing the risk of known attendant complications of immunosuppression such as malignancies and infection.

The use of induction immunosuppression in low risk kidney transplant recipients varies with different transplant programmes. Different studies in different environments have varying conclusions. While some argue for the use of antibodies as part of induction immunosuppression protocol, the prohibitive cost of these agents preclude their regular use in resource poor environments. There is also the argument about the cost benefit of the use of such expensive medications in recipients with low immunological risk in poor environments.

This review article critically reappraises the possible need for the use of induction agents in low risk kidney transplant recipients in Nigeria.

### **INTRODUCTION**

Kidney transplant is now generally accepted as the treatment of choice for patients with end-stage renal disease. (1) This is because of its association with improved survival and quality of life when compared with other forms of renal replacement therapy.

Immunosuppression has played a strong role over the years in improving the outcomes of renal transplant. The main aim of transplant immunosuppression is renal allograft survival in the long term and the patient survival while at the same time reducing the risk of known attendant complications of immunosuppression such as malignancies and infection.

Typically immunosuppression will involve the use of agents targeting different metabolic pathways and these agents are often used in combination. Using multiple agents in combination helps to improve the efficacy of immunosuppression and at the same time reduce the incidence of unwanted side effects of the respective agents. (2)

Three distinct phases are usually described in immunosuppression and these are: the induction phase, the maintenance phase and treatment of an established episode of acute rejection. (3)

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### **Goals of induction therapy**

The main goal of induction immunotherapy is the attainment of high level of immunosuppression at the time of the renal transplant in order to significantly reduce the risk of an acute rejection. Induction immunosuppression also helps in the optimization of outcomes in high immunological risk patients.

### **Indications of induction therapy**

Induction immunosuppression is not universally accepted as being mandatory but its use is common especially in patients considered as high risk. Patients of African descent and patients with preformed antibodies are generally high risk patients. (4)

### **Agents for induction immunosuppression**

There are different agents used for induction immunosuppression. The usual examples include antibodies which can pharmacologically be classified as monoclonal or polyclonal.

Mechanistically, these antibodies can also be further classified either as lymphocyte depleting agents or lymphocyte non-depleting agents. This differentiation is dependent on the ability of the respective agent to deplete T cells. (5)

### **Lymphocyte depleting Agents**

The lymphocyte depleting agents are Alemtuzumab, Antithymocyte globulin, and Muromonab-CD3. They exert their actions by causing T cell lysis and this leads eventually to the depletion of lymphocytes. There is an extensive release of cytokine that follows the administration of these agents as a response to cell destruction. This extensive cytokine release may cause significant adverse events.

### **Lymphocyte non-depleting agents**

Basiliximab and Daclizumab are lymphocyte non-depleting agents. These agents are able to prevent T cell activation and subsequent proliferation in the absence of cell lysis or destruction.

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Lymphocyte Depletin	Lymphocyte Non-depleting
Alemtuzumab	Basiliximab
Thymoglobulin	Daclizumab

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### **Polyclonal antibodies**

Polyclonal antibodies can be derived from the sera of horses or rabbits.

These agents influence different immune processes and ultimately lead to long term reduction in the number of T lymphocytes. Antithymocyte globulin is an example of a polyclonal antibody.

### **Dosage**

The usual dose of Antithymocyte globulin (equine) is 10-30mg/kg. This is administered as an infusion for 4-14 days, being given over 4-6hrs per dose. It is recommended to carry out an initial skin test prior to administration of the drug in order to detect any possible allergic reaction. The usual dose of Antithymocyte globulin (rabbit) is 1.5 - 2.5mg/kg/day for 3-10 days. (2)

Adverse effects may include cytokine release syndrome. The use of antihistamines and acetaminophen can help reduce these side effects. In the long term, patients may develop increased potential risk of opportunistic infection and post-transplant lymphoproliferative disorder.

### **Monoclonal antibodies**

Examples of monoclonal antibodies include basiliximab, daclizumab, alemtuzumab and muromonab-CD3.

Basiliximab is a modified chimeric antibody. These proteins have the ability to bind to interleukin-2 receptor (IL-2R), and thus prevent T cell activation and proliferation. The usual dose is to give basiliximab 20mg intravenously 2 hours prior to renal transplantation. A second 20mg dose is then subsequently given on 4<sup>th</sup> day post op. (2)

Daclizumab is also a modified chimeric antibody with efficacy similar to basiliximab, though potentially more costly. Its production has since been discontinued due to the high cost of production. (2)

Alemtuzumab is a humanized murine monoclonal antibody. Though the dosage varies, the common practice is to give it as 20-30mg intra operatively and post operatively on days 1 and 4. Side effects include pancytopenia, opportunistic infections and autoimmune anaemia.

Muromonab-CD3 is also a murine monoclonal antibody. It is also no longer available for clinical use.

### Glucocorticoid

Though rarely used for induction, steroids are still being used in maintenance immunosuppression. They are able to achieve their immunosuppressive effects through different pathways.

### Protocol For Immunosuppression In Renal Transplant At The Lagos State University Teaching Hospital (LASUTH) Ikeja Lagos Nigeria (Low Risk Group)

#### Immunosuppression

It is important to assess the immunological risk of the patient and document the following markers of immunological risk

- HLA match at HLA-A, HLA-B, HLA-DR
- Assess whether the patient is non-sensitized, sensitized or highly sensitized ( DSA/PRA level)
- Assess whether this is a first transplant, or whether the patient received previous transplant
- Find out about any previous multiple blood transfusions
- Previous parity for women
- Was there any previous transplant lost to acute rejection

#### Initial Immunosuppression

Since most of our patients are direct fee paying, cost considerations in addition to risk/benefit assessment is relevant in our patients in determining use of expensive immunosuppression regimen.

Our protocol will be to review consideration of immunological risk status, financial status of the patient and benefits of induction therapy and the most appropriate induction protocol selected for the patient.

#### Baseline Immunosuppression

*Priming Recipient* – this is done the night before surgery (8.00pm)

- Oral Myfortic 720mg night before surgery
- Oral Cyclosporine ( Neoral ) 5mg/kg PO stat

#### *Operation Day – Morning*

- Oral Myfortic 720mg stat
- Oral Cyclosporine ( Neoral ) 5mg/kg PO stat

- Oral Nystatin 100,000 units stat
- Oral antihypertensive drugs
- IV Rocephine 1gm stat

#### *Intra-operative Immunosuppression and diuretics (administered at reperfusion of the kidney)*

- IV Methylprednisolone 500mg
- IV Furosemide 20mg
- IV 20% Mannitol 100mls

#### Initial Immunosuppression

- Low risk patient (First Kidney Transplant, 0-DR mismatch, nocardiovascular disease, low risk of diabetes mellitus)
- Evening ( 8.00pm ) day before transplantation – ( cyclosporine - neoral 5mg /kg PO, Myfortic 720mg )
- Morning of the day of transplantation (6.00am) – ( Cyclosporine – neoral 5mg/kg PO, Myfortic 720mg PO)
- Intraoperative immunosuppression and diuretics given at reperfusion of the kidney) – IV Methylprednisolone 500mg IV, IV Furosemide 20mg, IV 20% Mannitol 100mls.
- In the evening ( 8.00pm ) day of the transplant operation ( Cyclosporine – Neoral 5mg/kg PO, Myfortic 720mg PO, IV Prednisolone 100mg )
- From Day 1 Post transplantation ( 8.00am and 8.00pm ) – ( Cyclosporine – Neoral 5mg/kg PO – target a trough cyclosporine level of 200-250µg/L, Myfortic 720mg PO, Prednisolone 20mg at 8.00am

Our choice of cyclosporine is mainly based on availability. Tacrolimus based immunosuppression can however be used.

#### The Controversies

The use of induction immunosuppression in low risk kidney transplant recipients varies with different transplant programmes. Different studies in different environments have varying conclusions. While some argue for the use of antibodies as part of induction

immunosuppression protocol, the prohibitive cost of these agents preclude their regular use in resource poor environments. There is also the argument about the cost benefit of the use of such expensive medications in recipients with low immunological risk in poor environments. Though most of the patients awaiting kidney transplant in our environment are high risk patient, (6), with increasing awareness, we now see a few low risk patients hence the debate over the possible use of induction agents in this group.

Generally, induction immunosuppression leads to better graft survival with the depleting agents showing better results than the non-depleting agents. (7) Though epidemiological and immunological risk considerations form the basis for the selection of induction immunosuppression therapy in most transplant programmes, the choice of the specific potent induction agent to be used still raises lots of questions that are yet to be answered. Part of this is because there is an increased cost in the short term with the use of these agents. More so, these agents are not without disturbing side effects such as increased risk of infection and malignancy. Hence some transplant centres are not keen on their use especially in the absence of robust data supporting long term graft survival advantage and there is therefore need for further studies (8).

Sollinger et al in 2001 had noted that the use of basiliximab had similar acute rejection rates in recipients of living related or cadaveric renal transplant similar to the use of anti thymocyte globulin (9). Brennan et al in 2006 showed that the use of rabbit anti thymocyte globulin as induction in high risk renal transplant patients was associated with a less incidence of rejection at one year compared with the use of basiliximab. This was however with cadaveric donors (10). Furthermore, Morton et al in 2009 in their review recommended the adoption of interleukin 2 receptor antagonist as induction immunosuppressive agent in kidney transplant recipients (11). Bamoulid et al more recently in 2016 noted excellent early results with the combined use of an antibody induction agent and the triple combination of a calcineurin inhibitor, an anti metabolite and a steroid and recommended the use of same in high risk renal transplant patients (12).

However, Martinez *et al* had in 2009 suggested that young low immunological risk transplant recipients who are already on a calcineurin inhibitor based immunosuppression like tacrolimus

should not be routinely placed on a basiliximab based regimen as this regimen is not cost effective in this group and its use cannot be justified (13). Similar to the 2009 study by Martinez *et al*, Jain *et al* more recently in 2017 also found no advantage with the use of basiliximab in immunological low risk transplant recipients who are already receiving triple immunosuppression with a combination of a calcineurin inhibitor, an anti-metabolite and a steroid (13,14).

The use and choice of immunosuppressive therapy vary with different regions and centres. Most kidney transplant centres in the United States have adopted one form or the other of a potent induction immunosuppressive regimen as the routine for their practice and the most common agents used are anti thymocyte globulin (rabbit) and basiliximab (15).

In contrast to the American practice, the use of agents such as anti thymocyte globulin is unpopular in kidney transplant centres in India particularly for the low immunological risk recipients. This is because the evidence in support of their use is not convincing and the fact that they are not cost effective and have considerable side effects are considered as important negatives. These potent induction immunosuppressive agents are thus generally avoided as cost saving measures and also in an attempt to reduce potential associated morbidities (16).

Other studies by several other authors also buttress the diversity in the use of induction immunosuppressive agents. Gabardi et al in 2011 in their studied population suggested that there was no induction immunosuppressive regimen that can be considered as being the standard for kidney transplant patients, and as such the choice of agent and regimen used will vary with the physician and transplant centre involved, though antithymocyte globulin (rabbit) was found to be the most commonly used agent (17). To add to the controversies surrounding the choice of the best immunosuppressive agents and regimen to use in kidney transplant patients is the fact that most of the quoted studies has involved a mix of patients with different immunological risks and these patients were also on different forms of maintenance immunological regimens which may all affect the long term outcomes of these patients (18).

Irrespective of the immunosuppressive agent or regimen adopted in one's practice, it is important that a proper patient and programme assessment is carried out with careful consideration to not just the

patient's immunological risk status, but to other factors such as cost effectiveness, potential side effects and presence of comorbidities (19). This is particularly important because paying attention to these comorbidities especially those related to cardiovascular disease, malignancy and infection has been shown to improve outcomes in kidney transplant patients and can potentially help reduce mortality in the long term (20). There are also suggestions of the importance of race in the choice of the best immunotherapy for kidney transplant patients and also susceptibility to side effects. For example post transplantation diabetes mellitus has been shown to be of particular concern amongst African-Americans (21,22). Also while there are studies that show no negative effect following withdrawal of steroids from the immunosuppressive regimens of African Americans especially in the short term, some other studies document a negative impact of such withdrawal in the long term and the need for close monitoring and surveillance (23,24,25,26).

### **Dosing**

Another important consideration in immunosuppression is the appropriate dosing regimen for different age groups. Dose variations of induction immunotherapy agents should be considered in elderly kidney transplant recipients as elderly patients may require less dose of immunosuppressive agents compared to younger cohorts in order to achieve the same result (27). There is also room for consideration of reducing the dose of calcineurin inhibitors in immunosuppression or opting for regimen without these agents because of their association with nephrotoxicity (28).

### **Side Effects**

It is equally important to consider the side effect profile of the induction agent used for immunosuppression. For example, the use of tacrolimus as primary immunosuppression when compared to cyclosporine leads to fewer acute rejections amongst renal transplant recipients but more cases of insulin dependent diabetes (29). Monotherapy with mycophenolate mofetil may also be considered both for induction and maintenance immunotherapy in selected kidney transplant recipients especially those receiving kidneys from marginal donors. This helps to reduce the risk of nephrotoxicity (30). Possible negative implications for wound healing should also be considered. Though the incidence of wound related

complications is low with the use of most new immunosuppressive agent, mycophenolate mofetil in particular has been identified as a risk factor (31). In addition, different induction agents have also been associated with different risk for Post Transplant Lymphoproliferative Disorders (PTLD) (32). Consideration of the side effect profile may for example encourage the use of Belatacept which is a costimulation blocker which achieves good levels of immunosuppression without the side effect of nephropathy induced by calcineurin inhibitors (33).

### **Future Prospects**

Looking to the future, the fact that there are no ideal immunosuppressive agents or regimens gives the opportunity for the development of new methods that may answer some of the lingering questions in immunosuppression for kidney transplant recipients with consideration being given to cell based therapies which may have the advantage of donor specific unresponsiveness amongst others (34). The use of autologous mesenchymal stem cells as induction therapy has been shown to result in fewer side effects when compared to the use of induction therapy with anti IL 2 receptor antibody (35). New opportunities also exist for immunosuppression with the use of pharmacogenomics with potential for further individualizing immunosuppression (3).

### **Limitations**

There is a paucity of publications on immunosuppression in kidney transplant in Nigeria. This is mainly due to the limited number of centres available for kidney transplant. Most of the studies on induction immunosuppression in low risk immunological kidney transplant patients have been in the developed countries with different recommendations. Some of these studies argue for the use of induction immunosuppression in low risk renal transplant recipients for example Laftavi et al found that the use of low dose rabbit anti thymocyte globulin for induction in low risk renal transplant patient had additional long term benefit without significant risk of malignancy or infection compared to the use of anti interleukin 2 receptor therapy (36). Also in a study group in which high immunological risk renal transplant patients were excluded, both basiliximab and anti thymocyte globulin were found to be effective at reducing acute rejection compared to the no induction group (37).

There is however little evidence to separate ATG and basiliximab in terms of outcomes. Al Najjar reported no long term difference between antithymocyte globulin and anti-IL-2 receptor monoclonal antibody when used for induction in low risk patients (38). Also both basiliximab and anti thymocyte globulin when used as induction immunosuppression agents in a sequential protocol in low immunological risk renal transplant patients had similar outcomes in terms of acute rejection, graft and patient survival, though the risk of adverse effect was less with the use of basiliximab (39). In addition, a retrospective analysis of a group of African-American renal allograft recipients showed that there was no major impact on graft outcome irrespective of which of thymoglobulin or basiliximab was used as an induction agent (40).

Some studies however suggest some benefit with the use of alemtuzumab. Hanaway et al demonstrated the advantage of alemtuzumab induction over conventional induction protocol in a low immunological risk patient group (41). A meta-analysis of 10 randomised control trials showed that induction with alemtuzumab reduced the risk of biopsy proven acute rejection compared with the use of basiliximab. The meta-analysis however did not find any statistically significant difference between the risk of biopsy proven acute rejection when alemtuzumab was used compared to when rabbit antithymocyte globulin was used (42). There was also no difference in the safety profile between alemtuzumab and anti thymocyte globulin for induction therapy though the rejection rates were better with alemtuzumab (43).

However, Taber *et al* noted that the use of alemtuzumab in high risk patients reduces the rejection rates to about the same at 3 years as the rates in low risk patients with either no induction or induction with anti IL 2 receptor antibodies (44). Knight et al recommended a combination of sirolimus with basiliximab for immunotherapy in low risk immunologic patients in though in cadaveric transplant (45).

In one of the few available Nigerian studies, Arogundade in 2011 in a 10 year review of kidney transplants found that the commonest immunosuppressive regimen used in Nigerian transplant centres included calcineurin inhibitor based triple drug therapy, the calcineurin inhibitor based triple drug therapy being used as induction and maintenance in 95.8% of the recipients while antibody

induction therapy was used in only 4.2% of the recipients (46).

The protocol in our centre at the Lagos State University Teaching Hospital does not contain any antibody induction agent. There is ample scientific evidence with the earlier mentioned references that these antibodies may not be needed in our low risk patients. Our induction immunosuppression regimen is similar to what obtains in most renal transplant centres in Nigeria but differ markedly with the American experience.

This is largely due to limitation of funds and local data to guide our practice.

### **CONCLUSION**

Induction therapy helps to improve short term outcomes by reducing risk of acute cellular rejection. The agents and regimens adopted depend on the preferences of the clinicians and institutions. The Antithymocyte globulin (rabbit) is still the most commonly used agent in the US but Basiliximab, even though not as potent, appears safer and is mostly used in low-risk patients.

There appears to be no convincing evidence for the use of these very expensive induction agents in low immunological risk kidney transplant recipients in our own resource poor environment with mainly fee paying patients who have no health insurance cover for their treatment. In any case, we have very limited experience with their use.

While the choice and practice of induction immunosuppression in low risk kidney transplant recipients may vary with different centres and different locations, there is a growing consensus that the decision is best when individualized, with consideration given to cost benefits, immunological risk, potential side effects and relevant local evidence in support of the practice. It is important to stress the need for further research in our environment in order to determine the best induction immunosuppression protocol for our own patients.

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