Introduction

To prevent these events, immunosuppressive protocols are designed to sensitize or form de-novo donor specific antibodies (DSA). The second strategy utilizes biologic antibodies to T cells combined with low doses of conventional drugs to achieve the same goal [10]. Induction immunosuppressive protocols are designed to minimize acute graft rejection through massive immunosuppression by various induction strategies and maintenance of induced immunosuppression with maintenance immunosuppression protocols. However, drugs employed in these protocols have severe toxic side effects. For instance, nephrotoxicity resulting from calcineurin inhibitors may lead to graft loss in the transplant patient. Also, severe immunosuppression and other side effects of immunosuppressant medications may lead to the death of the patient with a functioning graft as a result of opportunistic infections, malignancies and cardiovascular disease [5,6].

In the absence of tolerance to the transplanted kidney, all renal transplant patients would require immunosuppressive therapy to prevent allograft rejection and graft loss. The optimal immunosuppression regimen needs to be determined for the recipient of induced immunosuppression with maintenance immunosuppression protocols. However, drugs employed in these protocols have severe toxic side effects. For instance, nephrotoxicity resulting from calcineurin inhibitors may lead to graft loss in the transplant patient. Also, severe immunosuppression and other side effects of immunosuppressant medications may lead to the death of the patient with a functioning graft as a result of opportunistic infections, malignancies and cardiovascular disease [5,6].

Basiliximab induction protocols may offer cost–benefit advantages in resource constrained centers compared with currently used calcineurin based triple-drug therapy. The clinical and financial benefits of reduced acute allograft rejection rates, graft loss and the excellent side effect profile Basiliximab in renal transplant recipients, potentially outweighs the additional costs incurred in the management of higher acute rejection rates, and graft loss in calcineurin based triple-drug therapy.

This reflective review article, examines the possible role of Basiliximab induction protocol as a means of improving clinical outcomes of renal transplantation, in African transplant centres operating in financial constraint economies.
large number of randomized control trials and meta-analysis, induction therapy with biologic antibodies and conventional immunosuppressive medications have been found to be superior to conventional therapies alone in the prevention of allograft rejection and graft loss [11,12]. Determination of optimal immunosuppressive therapy in any recipient, however, would depend on the immunologic risk profile of the recipient [10].

Certain cohorts of recipients are categorized as high-risk with respect to the propensity for allograft rejection. These include recipients of African descent, children, and recipients who have been previously sensitized to HLA antigens through blood transfusions, multi-parity, or prior renal transplantation [13,14]. The aims of induction therapy in renal transplantation is to decrease the risk of acute allograft rejection and maintenance immunosuppression with the hope of improving clinical outcomes in the high risk recipients [10].

In Nigeria, the majority of renal transplant recipients are high risk patients in view of the race (African descent), multiple blood transfusions to treat symptomatic anaemia [15,16] and in some women, multi-parity. Most transplant centers in Africa operate in a resource constrained setting as the majority of patients undergoing renal replacement therapy pay out of pocket, with severe limitation on available funds for treatment [17]. Despite the limitations, transplant centers should aim at achieving clinical outcomes of renal transplantation that is comparable with those of centers in the developed economies.

Optimal induction protocol in this setting should be cost effective, taking into consideration the cost saving benefits of protocols that could reduce additional expenses incurred in the management of allograft rejection, graft loss, opportunistic infections and malignancies. This review focuses on the potential benefits of utilizing Basiliximab induction protocols in achieving internationally comparable outcomes for renal transplant recipients in the resource-limited economic setting of most African renal transplant centers.

**Immunosuppressive therapy in renal transplantation; a holistic view**

Clinical indications for immunosuppressive therapy are generally classified into three; Induction therapy, maintenance of immunosuppression and rescue therapy for an established rejection episode [18,19]. Induction therapy denotes the administration of potent immunosuppressive medications in the peri-operative period to achieve maximum immunosuppression at a period of the first contact with the donor HLA antigens. Induction immunosuppression is used to prevent early acute allograft rejection [7,20].

Following successful induction therapy, "host-graft adaptation" develops with a resultant decrease in donor-specific immunological responsiveness to the transplanted organ in the presence of continuing immunosuppression therapy [19,21]. In maintenance immunosuppression, less intense immunosuppressive protocols (compared with induction immunosuppression protocols) are required to achieve prevention of allograft rejection and graft loss. Maintenance immunosuppression is initiated at the time of transplant in conjunction with induction therapy when utilized. Dual or triple drug regimens are usually employed to ensure adequate immunosuppression while minimizing side effects associated with high doses of a single agent employed as monotherapy [8]. Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines recommends usage of a calcineurin inhibitor and an antimetabolite agent, with or without corticosteroid for maintenance immunosuppression in transplant patients [9].

Acute rejection episodes (cellular or antibody mediated) generally occur when immunosuppression becomes inadequate. This may result from inadequate medication compliance by the recipient, drug-drug interactions which reduce the efficacy of immunosuppression or aggressive immunosuppression reduction protocols. Acute rejection causes a decline in allograft function that is characterized by well-established pathological features on kidney biopsy. Intense immunosuppression is generally utilized in an attempt to salvage the allograft [10].

**Rationale for induction therapy**

In organ transplantation, a wide variety of injurious events occurs intra-operatively. These include ischaemia-reperfusion injury, endothelial damage and the traumatic exposure of tissues during surgery. The barrage of multiple antigens presented to the recipient cause very intense immunological reaction to occur at the time of transplantation. Thus, it is logical in the management of immunosuppression of the transplant patient, to aim at maximal immunosuppression in the peri-operative period when immunological stimulation is maximal. Thus, justifying the need for induction therapy [22].

**Induction immunosuppression agents**

Immunosuppressive agents used for induction therapy in renal transplantation are antibodies that either target specific antigens on the surfaces of recipient's T cells or act non-specifically on the recipient's immune cells. They are classified into lymphocyte depleting or lymphocyte non-depleting agents depending on the ability of the medications to target specific antigens on cell surfaces leading to a decrease in the cellular expression of the antigens or cause non-specific immunological destruction of the recipient's lymphocytes resulting in a reduction of their number [23].

**Depleting immunosuppressive agents in clinical usage include**

Monoclonal antibodies such as Muromonab- CD3 (OKT3) a murine monoclonal antibody (immune globulin G type 2a (IgG2a) antibody). OKT3 binds specifically to the epsilon component of a human cluster of differentiation (CD3) T lymphocyte receptor complex which is involved in T cell signalling and activation through calcineurin dependent pathway [24]. It has been withdrawn from the market due to the associate side effects. Alemtuzumab (Campath) is another depleting agent currently in use. It is an Immunoglobulin G class 1 (IgG1) humanized monoclonal antibody to rat anti-human CD52 [23].

Thymoglobulin is a depleting polyclonal heterologous antibody that binds to multiple T cell receptors and antigens that are involved in adhesion, antigen recognition and co-stimulation. Its depleting effect takes place within 24hrs of administration with a long half-life [23].

Non-depleting immunosuppressive agents include are Basiliximab and Daclizumab. Basiliximab is a chimeric (mouse-human) monoclonal IgG1 antibody to CD25. CD25 is the subunit of the IL-2 receptor, which is a binding site of IL-2 [25]. While Daclizumab, is humanized IgG1 anti-CD25 antibody that has a similar mechanism to...
Choice of induction agents in transplant protocols

In the light of advancements in the treatment of renal transplant recipients, considerable improvements have been achieved in the reduction of acute rejection rates and early graft losses in the current modern era of immunosuppression therapy [25,26]. Notable among factors that have made an impact in the short-term outcomes of allograft renal transplantation is the beneficial effects of induction therapy. When recipients treated with protocols incorporating induction agents are compared with those treated with standard immunosuppression without induction, induction protocols have significant beneficial effects on the rate of acute allograft rejections and short term graft survival [20,27].

Although historically, clinical immunosuppression was based solely on the efficacy of protocols on the reduction of acute allograft rejection, current protocols aim at additional goal of promoting long-term graft survival, while minimizing opportunistic infections, malignancies, and side effects. Hence, current induction protocols are based on assessed risk-benefit considerations for each patient [20,28].

Despite the fact that published data is in favour of using induction protocols in transplant patients for the reduction of acute allograft rejection, there is no general consensus on the protocol to be considered as a first line treatment [29]. This controversy results from the fact that the clinical studies on induction protocols were carried out on patients with different degrees of immunological risk, and also in a frame work of varying maintenance immunosuppressive regimens [25,29]. In general, lymphocyte-depleting antibodies are recommended for recipients with a high risk of rejection, while for low-risk patients, interleukin-2 receptor antibodies are preferred [30].

Choosing an induction protocol in the African setting requires careful focus on many other issues apart from the cost of induction agents. First, is the awareness of the fact that live – donor transplantation is the only available transplant programme in most African Centers, and for the majority of the transplant recipients, the opportunity for a second transplant in the event of graft failure is virtually non-existent. This is due to the usual catastrophic spending incurred during the process of obtaining the first allograft. Secondly, steroid resistant allograft rejection usually ends up in graft failure, as other anti-rejection drugs are not readily available in many of the African countries. Thirdly, diagnostic facilities for the detection of etiology of a failing allograft, detection of opportunistic infection and malignancies are generally inadequate in most African countries leading to delays in the recognition of these complications and poor outcomes. Lastly, the cost of treating the complications related to immunosuppression in patients already besieged with the burden of financing expensive maintenance immunosuppressive medications could sometimes be unaffordable to the patient.

Thus, transplant centers in Africa should focus on improvement strategies that could bring about successful outcomes comparable with what is obtainable in the more developed transplant centers, by utilizing cost effective protocols.

In our opinion, interleukin-2 receptor antagonist based induction protocol when initiated, may result in a comparative reduction in allograft rejection rates and graft loss with minimal risk of complications related to immunosuppression in the setting of inadequate diagnostic and therapeutic facilities available in many resource-constraint African transplant centers.

Comparative efficacy of basiliximab induction

Several studies and meta-analysis have compared Basiliximab induction with either no induction or other antibody induction protocols in various cohorts of renal transplant recipients [31,32-35]. In a chowhan analysis by Webster et al. [33] Basiliximab induction was found to confer a 28% reduction in biopsy proven acute rejection rate at one year compared with standard therapy. In addition, Graft loss was reduced by 25% over the same period [33]. Adu et al. [35] in a meta-analysis of studies using interleukin-2 receptor antagonist based induction protocols documented a 49% reduction of acute rejection rates at six months [35].

When compared with other induction agents, the efficacy of Basiliximab induction has been found to be comparable with lymphocyte depleting agents in terms of reduction in the rate of acute allograft rejection and one year graft survival rates [33,36-38]. The efficacy of Basiliximab induction in reducing allograft rejection and early graft losses has also been documented in different age groups [39,40], ethnicity [41-43] and donor characteristics [27] various maintenance immunosuppression regimens [33] and different immunological risk profiles [32].

Side effect profile

One clear advantage of interleukin-2 receptor antagonist based induction protocols is the favorable side effect profile compared with lymphocyte depleting agent based protocols [23,25,27,30,31,33]. Adverse drug reactions such as cytokine release syndrome, thrombocytopenia and leucopenia are more common with ATG and alemtuximab compared with Basiliximab [25,31,44]. In addition, the serious effects of profound immunosuppression (opportunistic infection and malignancy) associated with induction protocols using lymphocyte depleting agents are considerably much lower with Basiliximab induction [7,18,31,45,46].
As noted by Forae [47], laboratory results emanating from most African institutional laboratories lack consistency and accuracy, due to the myriad of fundamental challenges in the establishment and maintenance of quality assurance in these laboratories. In the context of making the diagnosis of opportunistic infections and malignancies in post-transplant recipients, most transplant centers rely heavily on laboratories outside their institutions for confirmation of diagnosis. In general, considerable delay usually occurs between presentation by the recipient and confirmation of diagnosis. Therefore, protocols with low rates of opportunistic infections and malignancy are preferable, given the circumstances of poor laboratory support in these settings.

**Economic considerations**

Several studies have shown the economic advantages of Basiliximab induction compared with antithymocyte globulin induction or no-induction protocols [48-51]. For instance, Keown et al. [48], observed an average cost reduction of approximately $4,554.00 in the first year of transplantation in a randomized, prospective, double blind study which employed an economic model to evaluate the economic benefit of Basiliximab induction. Sensitivity analysis showed that most of the savings were due to a reduction in the duration of hospital admissions and also in the cost of managing acute allograft rejection and graft loss. Similar observations have been made in Japan [52] and in the United Kingdom [50].

**Induction protocol in Lagos State University Teaching Hospital (LASUTH), Ikeja, Lagos: An African account**

In Nigeria, more than 95% of transplant centers use calcineurin-based triple drug induction regimens comprising Cyclosporine or Tacrolimus in combination with Azathioprine or Mycophenolate Mofetil (MMF) and Prednisolone [53,54]. One year graft and patient survival are 83.2% and 90.2% respectively [53]. This outcome is lower than outcomes reported in centers in more developed countries in which one-year graft survival is more than 98%.

The renal transplantation programme in LASUTH commenced in November 2015. Several factors were taken into consideration in the development of the immunosuppression protocol for the programme. Major factors taken into consideration were, Cost implications, the high immunological risk profile of the patients (Table 1 and 2) (African descent, multiple blood transfusions and multi-parity) and availability of drugs in the country. Our induction immunosuppression protocol consists of:

| Evening (8.00pm) day before transplantation | Cyclosporine (neoral) 5 mg/kg PO |
| Morning of the day of transplantation (6.00am) | Cyclosporine (neoral) 5 mg/kg PO |
| Intraoperative immunosuppression (given at reperfusion of the kidney) | Methylprednisolone 500 mg IV |
| In the evening (8.00pm) day of transplant operation | Cyclosporine (neoral) 5 mg/kg PO |
| From day 1 post-transplantation (8.00am and 8.00pm) | Cyclosporine (neoral) 5 mg/kg PO (Target a trough cyclosporine level of 200-250 µg/L) |

**Table 1: Immunosuppression (Protocol A): Low risk patient (1st renal transplant, 0- DR mismatch, no cardiovascular disease, low risk of diabetes mellitus).**

| Evening (8.00pm) day before transplantation | Cyclosporine (neoral) 5 mg/kg PO |
| Morning of the day of transplantation (6.00am) | Cyclosporine (neoral) 5 mg/kg PO |
| Intraoperative immunosuppression (given at reperfusion of the kidney) | Methylprednisolone 500 mg IV |
| In the evening (8.00pm) day of transplant operation | Cyclosporine (neoral) 5 mg/kg PO |
| Basiliximab (Simulect) 20 mg dissolved in 5 ml water for injection and then made up to 50 ml with 0.9% saline and given as an infusion over 30 minutes | 1st dose: Within 12 hours of return to the ICU/ward |
| | 2nd dose: day 4 |
From day 1 post-transplantation (8.00am and 8.00pm)

<table>
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<tr>
<th>Drug</th>
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<tr>
<td>Cyclosporine (neoral) 5 mg/kg PO (Target a trough cyclosporine level of 200-250 μg/L)</td>
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<tr>
<td>Myfortic 720 mg</td>
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<tr>
<td>Prednisolone 20 mg at 8.00am</td>
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Table 2: Immunosuppression (Protocol B): High-risk recipients Rationale for LASUTH's immunosuppression protocol

In developing our immunosuppression protocol, our first consideration was the availability of the immunosuppressive drugs in the country. Cyclosporine, Myfortic acid and Basiliximab (Simulect) are marketed by Novartis pharmaceutical company, a company with prominent representation in Nigeria. Thus, compared to other agents that are imported infrequently into the country by smaller pharmaceutical companies, constant availability of these agents is guaranteed.

The second consideration is the immunological risk profile of our recipients. As mentioned above, the majority of renal transplant recipients are high-risk patients in view of the race (African descent) and multiple blood transfusions to treat symptomatic anaemia [15,16]. Our immunological risk assessment of recipients comprises of evaluating ABO blood group compatibility, HLA matching and donor specific antibody (DSA) assay. Patients admitted into our programme are those who are ABO compatible, are HLA matched (0-0-0 mismatches) or with “favourable” HLA mismatches (0-DR mismatch), and with no significant DSA. Therefore, our programme is selective in terms of recipients' eligibility criteria.

Although renal registry data is lacking in most African countries [55,56]. Most centers (95.8%) in the country use high doses of calcineurin-based triple drug therapy as induction protocol. With only 4.2% using antibody induction therapy [53,54]. Outcomes have not been acceptable with one year graft and patient survival was 83.2% and 90.2% respectively compared with annual graft survival rates greater than 95% reported in some renal registries [57,58]. Although, several factors such as medication compliance, the number of mismatches and donor characteristics affect graft outcomes, the choice of induction therapy has been shown play an important role in graft survival [7,12]. Therefore, antibody based induction therapy may improve one year graft survival outcome in transplanted patients in our setting, in view of the high immunological risk profile of our transplant recipients.

Choice of induction agent: Basiliximab in high-risk patients

Our choice of Basiliximab induction in our center though primarily based on guaranteed availability, supportive evidence of its efficacy in renal transplant recipients of African descent are available in the literature [41]. Although, there is a paucity of data on the comparative efficacy of Basiliximab in renal transplant patients in Africa, published data on its use in African American suggest that Basiliximab use is associated with a reduction in acute rejection rates and allograft losses compared with no induction. For instance, in a retrospective study of 175 transplants in African Americans by Hammond et al. [41], patients induced with Interleukin -2 receptor antibodies had a significantly better 3yr survival rate compared with the group that did not receive induction therapy (85% Vs 68%, p=0.032). Other authors have documented a similar observation in recipients of African descent living in Europe [59].

Shortcomings of induction protocol in a financially constrained economy

The major challenge to Basiliximab induction in our setting is the cost implication. The current cost of two vials of Basiliximab in Nigeria is approximately £1,800.00. Since most of the patients pay out of pocket for medical services, affordability of the extra cost for the medication is an important issue. However, taking a holistic view of the total cost of transplantation, this additional cost of immunosuppression might be mitigated by the overall cost of treatment and admission in patients who develop acute allograft rejection, some of which could have been prevented by Basiliximab induction.

Available data indicates that close to 20% of the evaluated 143 transplanted patients in the country developed acute allograft rejection within in the first year of transplantation [53]. A number of these rejection episodes could have been avoided if antibody induction immunosuppression had been employed. In a meta-analysis of the clinical benefit of Basiliximab by Keown et al. [12], relative risk reduction of acute rejection episodes was found to 35% in the patients who received Basiliximab induction [12]. Extrapolating the data to this population, about 11 rejection episodes would have been prevented in the transplant recipients. A second reason for the use of IL-2 antibody induction in resource-constrained centers is the favorable side effect profile as post-transplant malignancies and infections have been documented to be fewer with the use of IL-2 antibody compared with depletion antibodies [33,34]. Furthermore, induction therapy enables the utilization of lower doses of calcineurin inhibitors and steroid, thereby minimizing nephROTOXICITY and cardiovascular side effects from their usage in maintenance immunosuppression [35,36]. Thus, induction therapy though economically burdensome in resource-poor centers, its clinical benefits may outweigh the additional cost. Further evaluation is however required to adequately assess the risk versus benefit ratio in our setting.

Exploration of possible ways to improve current practice in our Centre

Our center had the first transplant in November 2015. The major barrier to transplantation has been the availability of funds and a number of lessons have been learnt from the performance of the first procedure.

Need for an improvement in service delivery financing

A major challenge to the program is the inability of patients to afford the cost of transplantation. Estimated annual cost of medications in the first year of transplantation in our center is about £16,000.00. This in most instances would be paid out-of-pocket by the recipient as funding for transplantation in the country is mostly by out of pocket payment [53]. The implication of this to the success of transplant programmes in the country is grave. Very few patients are...
able to afford this conveniently without recourse to catastrophic spending. Currently, as part of our recipient evaluation procedure, we have incorporated the evaluation of patient's ability to afford the cost of operation without catastrophic expenditure. The inability of most of our patients to finance transplant operations has put a serious limitation to the number of transplant operations that could be performed at our center annually.

In other parts of the world, the cost of renal transplantation is covered in considerable part by government funding such as the Medicare or the total cost being borne by public funding, as it is the current practice in the United Kingdom, Italy and other developed countries [58-61]. The absence of governmental support for transplantation in our setting has necessitated exploring other means of funding such as private insurance, charitable organizations and fund raising campaigns.

Ensuring availability of other induction agents and supportive therapies

For a transplant programme to develop, and expand, adequate provision must be made to cater for as many patient characteristics/requirements as possible. Taking in highly sensitised patients or those with very high immunological risk profile into our programme is not advisable as the infrastructure and the available immunosuppressive medications are insufficient for managing the patients. For instance, only two centres in the country have functional plasmapheresis capability. The cost of treatment in these centers is exorbitant and out of reach of most patients. Thus, the available infrastructure, equipment and drugs limit the scope of our transplant programme.

Reduction in the rate of graft loss due to allograft rejection in renal transplantation depends not only on prevention, but also on the ability to establish its diagnosis early, and to institute appropriate therapy. Most antirejection drugs such as the lymphocyte depleting antibodies (Thymoglobulin and Alemtuzumab) recommended for treating acute rejection, especially in patients that do not respond to steroids are not readily available in the country. Therefore, each episode of acute rejection is usually an ordeal for both the patient and the renal care team. Urgent importation of the medications is usually required, which for many of the recipients is unattainable, with resultant loss of a salvageable kidney.

Research

The first renal transplantation was performed in Nigeria 16 years ago. Currently, there are about 10 transplant centers in the country. However, the annual rate of renal transplantation in the country is less than 40 transplants per annum. This low volume of transplant is largely due to the financial constraint because of lack of government involvement. Though the numbers are small, there is a need for research into transplantation in our setting with the aim of provision of answers to specific issues and problems of transplantation in the country.

Conclusion

The process of discovering an optimal induction protocol for renal transplantation recipients in transplant centers operating in resource-constrained economies in Africa is a major challenge. Non-depletional IL-2 receptor antibody based protocols may offer better clinical outcomes and overall better cost/benefit ratio in high-risk patients, compared with calcineurin inhibitor based triple therapy induction. Transplant centers working in such economies should aim at achieving internationally comparable treatment outcomes through the utilization of clinically proven cost-effective protocols and carefully structured realistic service delivery financing.

On balance, the cost benefits of reduced episodes of acute allograft rejection, fewer allograft failure and favorable safety profile of Basiliximab induction therapy may offset the additional financial burden imposed by non-induction protocols.

Take home messages

Developing immunosuppression regimen in resource-constrained economies should aim at achieving internationally comparable treatment outcomes through utilization of clinically proven effective protocols.

Basiliximab induction offers better treatment outcomes compared with calcineurin based triple drug induction therapy in terms of fewer allograft rejection and graft survival.

Cost/benefit advantage may favour the use of Basiliximab induction therapy in resource poor transplant centers as the extra cost incurred with the management of acute rejection may be eliminated in many transplant patients.

Ease of administration and convenient dosage schedule (Two doses) make compliance with medication easy.

Good side effect profile reduces the need for expensive laboratory investigations, which, the facility for carrying out most times, is unavailable at the centre.

References


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