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Review Article

Tailor-Made Induction Therapy in 'Low Risk' Renal Transplants; A South Asian Perspective

Abstract

Induction therapy has established itself as an integral component of modern-day renal transplantation. Carefully selected induction therapy helps not only to avoid early rejection of grafts but also allows grafts with delayed function to recover prior to introduction of potentially nephrotoxic immunosuppressants. While the place of induction therapy and reduction in early acute rejection is well established, its overall impact on long-term graft and patient survival is still unclear, especially in the 'low-risk' transplant recipient. Considering the substantial initial costs of induction therapy and their potential adverse reactions, transplant clinicians in developing countries have had to weigh the true advantages in induction against affordability and sustainability in the 'free' state health care systems. This review looks at the place of induction therapy in the current clinical setting with special emphasis on the 'low-risk' transplant candidates in limited resource settings.

Introduction

The global incidence and prevalence of Chronic Kidney Disease (CKD) and End Stage Kidney Disease (ESKD) have reached epidemic proportions. Although a global problem, its burden on health economy has had far more devastating implications in developing countries such as Sri Lanka. While boasting of far superior regional health indices in areas such as neonatal mortality and maternal mortality, the magnitude of CKD, ESKD and associated mortality in Sri Lanka remains relatively high [1,2].

Although nationwide renal registries in Sri Lanka are non-existent, the crude calculated incidence of ESKD in the different provinces is reported between 37-82 per one Million population [3]. It has also been reported that CKD and genito-urinary related hospital admissions in the country have almost doubled over the past two decades. Concurrently, the in-hospital mortality from CKD has increased to 9.1 from 2.6 per 100,000 population [4]. Some of the reasons for these disappointing results include; lack of adequate state sponsored renal replacement therapy, poor patient acceptance of peritoneal dialysis, relatively low rate of deceased donor organ donation and prohibitive costs of transplant immunosuppression.

Renal Transplantation (RT) remains the optimum treatment modality for ESKD. While surgical technique has shown only minor modifications, the dramatic improvement in overall outcomes of RT all over the world has been attributed to improvements in the transplant pharmacotherapy. Advances in transplant pharmacotherapy have aimed at achieving better graft and patient survival, minimization of graft rejection and avoidance of significant adverse effects. In this regard, numerous new pharmacological agents have been introduced to maximize the graft and patient outcomes. Nevertheless, in the developing world, transplant clinicians face a constant battle in their attempt to maintain comparable outcomes amidst numerous socio-economic restrictions. Foremost among these restrictions come the relatively poor health care infrastructure beyond the tertiary hospitals and the limited public health funding.

Induction Therapy in Modern-Day Transplantation

Transplant pharmacotherapy consists of three chief components; induction therapy, maintenance immunosuppression and treatment of established rejection. Induction therapy is now recommended for all transplants with potential benefit over no induction in terms of reducing biopsy proven acute rejection (BPAR) [5,6]. The United Network for Organ sharing (UNOS) registry data also showed that induction with any of the commonly used agents contributed to better short-term and long-term allograft and patient outcomes [7]. The aim of induction therapy is to achieve an intense and selective suppression of the immune system at the time of graft implantation and immediate post-transplant period to minimize the incidence of early acute rejection [8].

Numerous biological agents have been introduced and are used as induction agents in RT. The choice of which induction agent to use depends on different factors including degree of immunological risk, local availability, cost and clinician familiarity. Over the last two decades, there has been a steady increase in use of induction agents for RT across the world. Andreoni et al (2007) reported that over 74% of centers in United States used induction therapy for transplantation by 2004 [9]. UNOS Registry data showed that the different agents used for induction were; rabbit anti-thymocyte globulin (rATG) 39%, interleukin-2 receptor antagonists (IL-2RA) 28%, alemtuzumab 9% and equine anti-thymocyte globulin (eATG) <2% [10]. However, outside the United States, this trend is different with IL-2RA being the commonest induction agent among most transplant centers [11].

Deciding on the Induction Therapy

Assessment of pre-transplant immunological risk of a given recipient helps in the decision regarding induction therapy. The highest benefit of induction therapy is seen among patients with higher risk of acute rejection [5]. 'High risk' is defined by the presence of characteristics such as young recipient age, older donor age, presence of preformed antibodies, re-transplantation, poor human leucocyte antigen (HLA) match, prolonged cold ischaemia (>24 hours), donation after cardiac death, extended criteria donors and recipients of certain races known to have increased immunogenicity (eg. African-Americans) [12–15] (Table 1).

Induction agents in current practice have demonstrated a significant definitive reduction in incidence of acute rejection and early graft loss [16,17]. An additional advantage of certain induction therapies is the ability to delay the introduction of potentially nephrotoxic calcineurin inhibitors (CNI) as maintenance therapy. This is especially useful in deceased donor RT with delayed graft function, where CNI therapy can be delayed until some recovery of the graft is obtained [18,19]. While the overall benefits of induction therapy are well documented, they also have inherent adverse reactions including infection and malignancy secondary to the potent inhibition of host immune responses [20,21]. Hence, clear identification of induction agent to be used in each individual patient need to be defined using a careful risk-benefit assessment.

The commonly used induction agents include monoclonal antibodies; mAb (muromonab-CD3, daclizumab, basiliximab, alemtuzumab) and polyclonal antibodies; pAb (ATG [equine / rabbit]) [22,23]. These are further classified based on their effect on the host T cells; T cell depleting agents (alemtuzumab, ATG, and muromonab-CD3) and T cell non-depleting agents (basiliximab and daclizumab) (Table 2).

T-Cell Depleting Agents

These induction agents act by depleting the circulating host T lymphocytes. Extensive T cell destruction may result in the release of cytokines that mediate a 'serum sickness type' reaction with significant adverse effects to the drug. The

Table 1: High risk characteristics (for acute rejection) in renal transplantation (5).

- Young recipient age
- Older donor age
- Re-transplantation
- Extended criteria donors
- Deceased donors after cardiac death
- Poor HLA match
- Prolonger cold ischaemia
- Preformed donor specific antibodies
- Delayed graft function
- African Americans

Table 2: Characteristics of T cell depleting/ non-depleting induction agents.

T cell depleting agents	T cell non-depleting agents
Causes actual lysis of T cells and their destruction	Inhibits the T cell activation pathway without their actual lysis
	Cytokine release does not occur and thereby minimal adverse
Cell lysis results in the release of cytokines and associated adverse reactions	reactions
Higher potency	Lower potency
	To be used in low immunological risk recipients
To be used in high immunological risk recipients	
Profound immunosuppression allows delayed introduction of CNI	CNI cannot be delayed
Higher incidence of infection and post-transplant malignancy	No significant increase in risk of infection or malignancy

resulting T cell depletion is long standing and may even be permanent in elderly patients, results in a chronic increased susceptibility to infections and malignancy [24,25]. The commonly used T cell depleting agents include anti-thymocyte globulin (ATG), muromonab-CD3 and alemtuzumab.

Antithymocyte Globulin (ATG)

ATG is acquired by injecting either horses or rabbits with human lymphoid tissue and harvesting the resulting antibodies to make equine (eATG) or rabbit (rATG) respectively. ATG induction therapy causes host T cell depletion by a combination of cell lysis and clearance by the reticulo-endothelial system. The overall result is a profound suppression of host cellular and humoral immunity [26].

Immediate adverse effects related to ATG are caused by the cytokine release phenomenon. This involves a combination of constitutional symptoms including fever, chills, headache, nausea, diarrhea, malaise and dizziness that is often poorly tolerated by the patient. The intensity of these adverse reactions can be suppressed by antihistamine and acetaminophen premedication. Furthermore, it is recommended to be administered via a central line, to minimize thrombotic complications of the access route [27]. Serious bone marrow suppression with leukopenia and thrombocytopenia has also been reported in up to 30% of recipients [28].

ATG treatment is initiated at or just before the time of graft implantation and may consist of 5-7 divided doses. Based on the findings of a landmark study by Brennan et al (1999), rATG remains the preferred agent over eATG [29,30]. Results of the study showed significantly lower incidence of BPAR

with rATG compared to eATG (4% vs 25%). The overall 1-year graft survival was 98% with rATG compared to 83% with eATG ($p = 0.02$). However, rATG was associated with a significantly higher incidence of leukopenia (56%) compared to eATG (4%), ($p < 0.0001$). Nevertheless, the overall incidence of infections was not significantly increased with rATG. Interestingly, the incidence of post-transplant cytomegalovirus infection was in fact lower with rATG (12.5%) compared to eATG (33%), ($p = 0.025$). There was no significant difference between the two with regard to incidence of long-term post-treatment malignancy [31]. A 10-year follow up study between the two preparations also showed significant advantage of rATG in all composite end points including overall event-free survival [32].

Despite the proven efficacy in reducing BPAR, the sustained and profound immunosuppression caused by T cell depletion have had significant drawbacks in terms of long-term safety. In a study looking at over 73,000 transplants in the United States between 1988 and 1997, ATG was associated with increased post-transplant mortality both in early and late follow up. The early deaths were attributable to infection and cardiovascular morbidity while the late post-transplant deaths were mainly due to malignancy [33].

In other studies, ATG use has shown significantly lower rates of BPAR compared to no induction across all transplants albeit with no difference in graft or patient survival [34,35]. This advantage was also seen among highly sensitized and 'high risk' recipients, making ATG the induction therapy of choice in such patients [36,37]. Therefore, considering the adverse effect profile of ATG, it is mostly reserved for transplants categorized as 'high risk' of early rejection [5].

Alemtuzumab

Alemtuzumab is a mAb originally produced for treatment of chronic lymphocytic leukaemia. It is an anti CD-52 antibody which acts against the CD-52 molecules present on a variety of immune modulatory cells including B cells, T cells, macrophages and natural killer cells [38]. The resultant reaction causes immune cell lysis with effects often lasting up to one year. Profound and sustained immunosuppression with alemtuzumab is often used to minimize other maintenance immunosuppression, thereby contributing to lower overall cardio-vascular morbidity [38]. The commonest adverse effects include bone marrow suppression (40-70%) affecting all three cell lines along with constitutional symptoms such as vomiting, diarrhea and headache [39]. These effects can be quite profound requiring mandatory premedication with antihistamines, steroids and acetaminophen [40,41].

There has been an increasing trend for the use of alemtuzumab for transplants especially where early steroid withdrawal (ESW) or CNI minimization have been planned. Hannaway et al (2011) compared alemtuzumab induction with rATG and basiliximab across different risk categories, and found lower incidence of BPAR with alemtuzumab compared to basiliximab in 'low risk' transplants, without any observed advantage in graft or patient survival [42]. In the 'high risk'

patients, alemtuzumab showed no significant advantage over rATG.

In another review comparing ATG with alemtuzumab for transplants where ESW was carried out, alemtuzumab showed lower incidence of BPAR at I-year compared to ATG. Among 6 studies that compared these two modalities, the above finding was seen in 4 studies while the other two studies showed equivocal results [35].

There are differing dosing schedules of alemtuzumab from a single dose to two doses. The single-dose regime involves an intra-operative dose of 30 mg given subcutaneously as opposed to the two-dose regimen where a second dose may be given on day-01 or day-04. The single-dose subcutaneous administration as opposed to the intravenous route is considered a compromise between desired immunosuppressive effect and adverse reactions [43].

Muromonab-CD3 (OKT3)

Muromonab-CD3 was the first biological agent used in transplantation. It was initially developed for treatment of BPAR and was later used as an induction agent. It is an anti-CD-3 antibody and binds to the CD-3 receptor on the surface of T cells. Despite encouraging early results, its clinical use soon waned due to the potential life-threatening adverse effects and costs, resulting in its discontinuation.

T-Cell Non-Depleting Agents

Basiliximab: Basiliximab is a mAb and an interleukin 2 receptor antagonist (IL-2RA). Its binding to the CD-25 molecule of the IL-2 receptor causes inhibition of T cell activation and subsequent proliferation without actual T cell lysis [44]. The resulting IL-2 binding saturates the relevant receptors thereby inactivating the T cells for up to 8 weeks [16]. Basiliximab is a genetically modified mAb where majority of the original murine amino acids have been replaced with human amino acids, being referred to as a chimeric antibody with 70:30 human and murine components. The presence of human protein confers lower immunogenicity resulting in reduced allergenic reactions.

Basiliximab is given as a two-dose regime; first dose given approximately 2 hours before implantation and the second dose given on day-04. The absence of actual T cell lysis avoids the cytokine mediated 'serum sickness type' adverse effects seen with ATG. Furthermore, the T cell non-depleting nature prevents any appreciable increase in post-transplant infection or malignancy, making it one of the safest induction agents in use [16]. While no major adverse effects have been reported over placebo drugs in clinical trials, the only significant adverse effect reported is hypersensitivity reactions (<1%) [45].

The actual drug to drug cost of basiliximab is higher compared to ATG. However, when considering the greater number of doses required with ATG and the overall costs to avoid and manage adverse reactions, basiliximab has been more economical than ATG. In a study conducted in the United States by Lilliu et al (2004), the average cost saving per patient

when using basiliximab instead of ATG was 1459 U.S dollars [46]. Furthermore, the use of basiliximab over placebo has also proved cost effective considering the advantages of reduced incidence of BPAR and its management [47].

Daclizumab: Daclizumab was the first IL-2RA used in induction. Its function, efficacy and adverse effect profile was similar to basiliximab with no significant difference in BPAR or overall outcomes [48]. However, daclizumab was associated with significantly higher production costs and technical demands compared to basiliximab. In the absence of any advantage over the cheaper and simpler alternative of basiliximab, daclizumab fell out of favour among clinicians and eventually was withdrawn from the market in 2009.

IL-2RA have shown a significant reduction in BPAR as well as improved graft outcomes compared to placebo in a comprehensive Cochrane review looking at over 30 randomized controlled trials [49]. The same review also showed no increase in the incidence of malignancy although it did not show any advantage of IL-2RA in all-cause mortality. A similar review of results from Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) also showed a 26% reduction of BPAR with basiliximab over placebo in patients given cyclosporine maintenance, although this advantage was not seen in 'low risk' patients given tacrolimus based maintenance [50] (Table 3).

Discussion

Induction therapy is an integral part in the current management of peri-transplant immunosuppression. Induction therapy has resulted in a significant reduction in BPAR and an overall improvement in short term and possibly long-term graft survival, especially in 'high-risk' recipients [7]. The different induction agents available in current practice have differing immunosuppressive potencies, adverse effect profiles and cost implications. Therefore, the choice of induction agent and its dosing schedule is often individualized according to the recipient immunological risk, clinician familiarity and affordability in the local set up. These factors become even more important in the developing world where the transplant teams face a constant battle to achieve comparable results amidst limited funding and resources.

Cost Implications of Induction

Outside the United States, basiliximab remains the commonest induction agent used in modern day practice. When comparing basiliximab, rATG and no induction, with standard maintenance therapy, basiliximab was the only regimen found to be cost-effective at £ 20,000 and £ 30,000 of quality adjusted life years in the United Kingdom [51,52]. The same study also found that rATG was not cost-effective at the above determined economic parameters. Basiliximab was found to be more cost-effective owing to lower medicinal costs as well as the reduced cost of ancillary treatment required as infection prophylaxis and management compared to rATG. Although the reduced incidence of BPAR with rATG made the cost comparison closer, the overall costs were still higher compared to basiliximab [52]. Similar cost-effective outcomes of basiliximab over rATG were found in other studies across United States, Canada and France [46,53,54]. Although a similar cost and economic evaluation of immunosuppressive therapy is not available in the South Asian region, the overall trend is likely to be quite similar.

The 'Low-Risk' Recipient and Induction

Although the advantage of induction therapy in all transplants have been shown in the Western literature including the UNOS registry, its role in the 'low risk', live donor, primary transplant recipient has not been quite conclusively proven. Furthermore, most of the recommendations for routine induction therapy in all forms of RT have been based on relatively obsolete data from studies which did not use the current best triple regimen maintenance immunosuppression [55]. With this current tacrolimus based triple drug maintenance therapy, the addition of induction may contribute to reduction of BPAR by only 1-4% and with no appreciable advantage in graft or patient survival. A retrospective study based on Organ Procurement and Transplant Network (OPTN) data studying the place of induction in 'low risk' live donor transplants, failed to show any significant reduction in BPAR or graft loss at 5 years [56]. Another retrospective analysis by Tanriover and colleagues (2015) from the same registry data of more than 35000 live donor transplants with tacrolimus based triple immunosuppression, failed to show any advantage of IL-2RA in terms of BPAR or graft survival [57]. Lim and colleagues (2009) have also reported similar observations in Australasia. Data from ANZDATA registry for 'low risk' transplants (primary transplants with <2/6 HLA mismatches) with tacrolimus based maintenance therapy, showed no advantage of IL-2RA in reducing BPAR [50].

Table 3: The commonly used induction agents.

Agent	Monoclonal/ polyclonal	Mechanism of action	Duration of effects	Adverse effect profile
Basiliximab	mAb	IL-2RA Binds to CD25 in activated T cells	Several weeks	No cytokine release effects No proven increase in incidence of infection / malignancy Rare hypersensitivity reactions (<1%)
rATG	pAb	Widespread inactivation and destruction of T cells	Months to years	Massive cytokine release effects Serum sickness like disease Thrombocytopaenia Infusion reactions
Alemtuzumab	mAb	Binds to CD52 on naïve T cells, some B cells, macrophages and natural killer cells	Months to years	Cytokine release effects Bone marrow suppression with pancytopaenia Infusion reaction

The South Asian Perspective

There remains a relative scarcity of data for induction therapy concerning RT in South Asia. A few smaller studies from India and Sri Lanka have looked at the effect of induction therapy on live donor transplants using tacrolimus based triple therapy maintenance immunosuppression. They observed no significant advantage of IL-2RA induction in terms of BPAR or graft/ patient survival in 'low risk' live donor transplants [58,59]. A review and cost analysis by Wiseman (2015) concluded that with a modern-day acute rejection risk of <10% in 'low risk' live donor transplants, the sample of patients needed to be treated with induction therapy to show a statistical and clinical advantage was too large and too expensive [60]. The review described that to avoid one episode of BPAR it would require induction of 33 such patients, with no clear benefit of long-term outcome. Therefore, the place of expensive induction therapy in the 'low-risk' live donor transplant candidate remains inconclusive especially in the context of limited-resource transplant centers in South Asia.

Induction Therapy in Sri Lnaka

Alemtuzumab is not freely available in Sri Lanka and has been used only sporadically. Although both rATG and basiliximab are available, the head to head costing of the agents compares quite favourably with basiliximab, making it the induction agent of choice among transplant centers in the country. Basiliximab is also the only induction agent provided by the Ministry of Health, under the free state-run health care system. The safety profile of basiliximab in term of post-transplant infections is an added advantage in the local set up considering the excess cost implications of managing such infections. Nevertheless, further limitations do exist.

Basiliximab made available in the state health sector is often inadequate to meet the demand of all transplants that take place, resulting in a significant disparity between demand and supply. Often, transplant centers have had to make their own individual protocols to suit the local immunological risks and stay within the allocated institutional budgets. One such individualized protocol involves the use of a single dose of basiliximab instead of the usual two doses in the 'low risk' patients. Cunningham and colleagues (2016) have published their own experience with a single dose basiliximab protocol and reported no demonstrable difference in the rate of BPAR, graft survival or patient survival in over 760 patients [61].

1. The National Institute of Nephrology and Transplant, Colombo is the only dedicated transplant hospital in Sri Lanka, performing approximately 30% of all state sector transplants in the country. Pre-transplant donor specific antibody screening is not available in the state-run transplant system. Our current protocol of induction is as follows.rATG for all re-transplants and 'high-risk' transplants (live or deceased donor) with HLA 6/6 mismatch

2. Basiliximab two doses (day 0 and 4) for all other deceased donor transplants

3. Basiliximab two doses (day 0 and 4) for all other live donor transplants considered 'moderate risk' (HLA mismatch 3-5/6)

4. Basiliximab single dose (day 0) or no induction for 'low risk' (live donor, HLA mismatch 0-2/6, recipient >30 years and donor <60 years)

All patients are given standard triple therapy of steroids, mycophenolate and tacrolimus for maintenance immunosuppression. The small geographical extent of the country has allowed closer surveillance of such patients who are transplanted without induction and allowed in the achievement of satisfactory and comparable outcomes.

Conclusion

The use of biological agents as induction therapy has steadily increased all over the transplant world in recent years. Induction therapy has shown a clear benefit over no induction in reducing BPAR after RT, paving the way for their introduction in to most transplant protocols. However, there remains considerable skepticism and a lack of robust data to confirm its advantage in terms of long-term graft and patient survival as well as its benefit in recipients at low immunological risk. In addition, the associated costs and potential adverse effects have prevented induction therapy from being incorporated routinely in all categories of renal transplants in the developing world. This has led to a new paradigm of immunological risk stratification among transplant recipients and making individualized protocols based on potential advantage over risk and affordability in the health care economy. In the absence of level-1 multicenter randomized clinical trial evidence of clear benefit in the patients with low immunological risk, the selective use of induction therapy in 'moderate' to 'high risk' patients and induction sparing in 'low risk' patients appear justifiable.

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