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Induction Agent in Low Immunological Risk; the Indian Scenario

Abstract

Chronic kidney disease (CKD) is a global health problem because of increasing prevalence, high cost of management and risk factor for ischemic heart disease. Renal transplantation remains the current best form of therapy for end stage renal disease (ESRD). Renal transplantation with living kidney donor is better compared to deceased donor transplantation in terms of survival and quality of life. Use of induction agents in renal transplantation has evolved over the years from initial use of muromonab, anti-thymocyte globulins (ATG), and IL-2 blockers to alemtuzumab. Multiple studies have compared these agents in different risk groups and scenarios. There is strong evidence for using ATG compared to IL-2 blockers in high risk group, however, the same does not apply to low risk group. There is a paucity of data regarding the use of induction agents in the Indian sub-continent. The role of induction agents in this population which is prone to opportunistic infections, side effects of drugs and where cost of treatment takes a priority, are not well known especially in low immunological risk group. This review article summarizes the role of various induction agents in different risk groups with relevance to Indian population.

Keywords: Induction; ATG; Basiliximab; Renal; Transplantation and low risk; India; Population

Review Article

Volume 3 Issue 6 - 2016

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Received: August 04, 2016 | **Published:** December 12, 2016

Abbreviations: CKD: Chronic Kidney Disease; ESRD: End Stage Renal Disease; ATG: Anti-Thymocyte Globulins; RRT: Renal Replacement Therapy; CAPD: Continuous Ambulatory Peritoneal Dialysis; CNI: Calcineurin inhibitors; ATG: Anti-thymocyte Globulin; rATG: Rabbit Anti-thymocyte Globulin; ALG: Anti-lymphocyte Globulin; ARDS: Acute Respiratory Distress Syndrome; CMV: Cytomegalovirus; BPAR: Biopsy Proven Acute Rejection; MMF: Mycophenolate Mofetil

Introduction

India faces an uphill task of providing affordable tertiary health care to its citizens due to lack of public infrastructure. The crude age adjusted incidence rate of end stage renal disease (ESRD) in India is 151 per million population [1,2]. According to the Indian CKD registry, about 74.5% of patients do not receive any form of renal replacement therapy (RRT) and only 2.5% receive renal transplantation. It has been estimated that about 90% of ESRD patients die within months of diagnosis in south Asia as patients cannot afford such treatments due to poverty [2].

ESRD patient's have2 options: maintenance dialysis (haemodialysis or peritoneal dialysis) or renal transplantation. Those patients who are fit enough, renal transplantation are the best option when compared to dialysis in regards to patient outcomes and cost. A recent study (2015) done by Diego Rosseli [3] concluded that renal transplantation, from a living or deceased donor, improves the overall survival rate and quality of life and is a cost saving alternative compared with dialysis. Renal transplantation living or deceased donor improves both life expectancy and quality of life for the recipient and can be done with living or deceased donor. Patient and graft survival is better by a transplant from a living donor than from a deceased donor. It is estimated that in India 15,000 patients commence maintenance haemodialysis, 3000 new patients choose continuous ambulatory peritoneal dialysis (CAPD) and 3500 patients undergo renal transplantation every year [4]. It is estimated that in India 150,000 people are waiting for renal transplantation and 90% of patients in waiting list die without getting an organ transplant [1].

The corner stone of renal transplantation is the use of immunosuppression to modify the alloimmune response to 'the foreign body' i.e. 'renal allograft. Since the time of first successful human renal transplantation among twins in 1954 there have been lots of advances in the field of use of immunosuppressant. The era of immunosuppressant began (1960s) with the use of steroids followed by use of combination of steroids and azathioprine. Introduction of calcineurin inhibitors (CNI) and induction agents (depleting and non-depleting) have remarkably decreased the rate of acute rejection however with little effect on long term out comes. (Table 1) lists the immunosuppressant medication used in renal transplantation

Induction drugs

Induction agents are immunosuppressive drugs which are given during the peri-transplant period with the intention of decreasing the rate of acute rejection. The choice of induction regimen varies from transplant centre to centre and individual to individual. Initial induction agents in 1990s were OKT3 and

horse ATG, both of which have decreased significantly over the years. Commonly used induction agents are equine ATG and IL-2 receptor blockers. They can be classified as T cell depleting and T cell non-depleting. T cell depleting agents are most commonly used followed by basiliximab according to US data 2009 (Table 2-4).

Table 1: The list of immunosuppressive medication used in renal transplant.

Induction agents	ATG (anti-thymocyte globulin)
	Basiliximab
	Daclizumab
	Alemtuzumab
	Rituximab
Maintenance agents	Corticosteroids
	Mycophenolate mofetil (MMF)
	Azathioprine
	Tacrolimus
	Cyclosporine
	Belatacept
	Sirolimus

Table 2: lists a variety of induction agents used in renal transplantation.

Generic	Brand	Classification	FDA indication	FDA Approval	Manufacturer
Basiliximab	Simulect	IL-2 receptor antibody, monoclonal antibody, CD25	Prevention of rejection in kidney and liver transplant	1998	Novartis
Daclizumab	Zenapax	IL-2 receptor antibody, monoclonal antibody, CD25	Prevention of rejection in kidney transplant	1997-2009	Roche
Rabbit ATG	Thymoglobulin	Polyclonal anti-T cell	Treatment of acute rejection in kidney transplantation	1998	Genzyme-sanofi
Horse ATG	ATGAM	Polyclonal anti- T cell	Treatment of acute rejection in kidney transplantation Aplastic anaemia	1981	Pfizer
Alemtuzumab	Campath	Monoclonal antibody, CD52	Treatment of B cell CLL	2001-2012	Berlex laboratories
Muromonab, OKT3	Orthoclone	Monoclonal antibody, CD3	Treatment of acute rejection in liver, heart, kidney transplantation.	1986-2009	Janssen-cilag

Table 3: Classification of induction agents.

Agents	Example
1.T cell depleting	Anti-thymocyte globulin (ATG)
2.T cell non depleting	IL-2 receptor inhibitor e.g. basiliximab

Citation: Shenoy P, Bridson JM, Halawa A, Sharma A (2016) Induction Agent in Low Immunological Risk; the Indian Scenario. Urol Nephrol Open Access J 3(6): 00106. DOI: 10.15406/unoaj.2016.03.00106

Table 4: Immunoglobulin's available for induction in renal transplantation.

	Atgam	Lymphoglobulin	Thymoglobulin	ATG-Fresenius
Manufacture	Pfizer	Various	Genzyme-sanofi	Fresenius-biotech, GmBH
Location	New York, USA		Cambridge, USA	Grafelfing, Germany
Species	Horse	Horse	Rabbit	Rabbit
Concentration (mg/ml)	50	10-20	5	20
Immunogen	Human thymus	Human thymus	Human thymus	Jurkat lymphoblastic cell line
Dosage per day (mg/kg)	10-30	10	1.25-2.5	1-5

Muromonab

Muromonab (OKT3) is a monoclonal antibody derived from mice which binds to CD3 receptor. It was initially used for induction. It is given in a dose of 5-10 mg/day for about 10-14 days with cumulative dose of 70mg. Common side effect include cytokine release syndrome with fever, chills, nausea and vomiting. Cytokine release may lead to pulmonary edema and hemodynamic instability that is more likely in those who have fluid overload. Few patients have developed anti-mouse antibodies following muromonab infusion. Consequently, Muromonab is rarely used nowadays for induction in renal transplant.

Anti-thymocyte globulin

Anti-thymocyte globulin (ATG) is produced by immunizing animals with human thymus derived lymphoid cells. They are commercially available in 4 forms, with rabbit anti-thymocyte globulin (rATG) being more efficacious, hence it is the preferred choice over equine anti-lymphocyte globulin (ALG). ATG is not FDA approved for induction in renal transplantation; however, it is used rather commonly in North America. Various regimens use daily intravenous preparation for 5 to 10 days either for induction or for treatment of steroid resistant rejection usual dosage is 1.5 mg/kg for 3-5 days [5-14].

High cumulative dose of ATG and long duration of treatment is associated with opportunistic infection and malignancy, however, lower dose (<3mg/kg) may be insufficient to prevent acute rejection [15]. ATG contains multiple antibodies which bind to variety of cells in the body including red blood cells, white blood cells, endothelium and platelets. ATG is one of the most potent immunosuppressive agents available and can suppress lymphocytes for up to 24 hours. Being non-specific, ATG leads to marked immunosuppressive effect that predisposes to infection and malignancy. Most common side effects are infusion reactions including fever, chills, lymphocytopenia, pancytopenia and rarely acute respiratory distress syndrome (ARDS). Cytopenias require dose adjustment and dose of ATG can be modified based on CD2 and CD3 counts. Peripheral administration of ATG can lead to venous thrombosis which can be reduced by concomitant infusion of heparin and hydrocortisone [16,17].

Alemtuzumab

Alemtuzumab or Campath-1H is a monoclonal antibody against CD 52. CD 52 is present on most of the lymphocytes B and T cells and monocytes but not on hematopoietic precursor cells. It's not FDA approved for induction and is used as off label drug. It suppresses lymphocytes for many months to years and is given in a dose of 30 mg or 0.3mg/kg IV in a single dose, or sometimes two doses based on lymphocyte count [18]. Common side effects include cytokine release syndrome as can be seen with ATG, however to a lesser extent. Its use has been associated with infectious complications and autoimmune thyroiditis and has been used to treat acute rejection in post transplant scenario with poor outcomes. The initial use of alemtuzumab in renal transplant recipients was associated with intense and prolonged lymphocyte depletion, increased late antibody-mediated graft rejection and increased rates of serious infection [19-22].

IL-2 Inhibitors

IL-2 is highly expressed in activated T cells. IL-2 inhibitors (basiliximab and daclizumab) bind specifically to its alpha subunit (CD25) and block further activation of T cells. Basiliximab is a chimeric antibody which can suppress T cell for up to 25 to 35 days. It issued for induction regimen only. Normally it is given in a dose of 20 mg on the day of transplantation and day 4 of post transplantation. No major side effects have been reported with basiliximab. It's the only induction drug which is FDA approved

Evidence for various induction regimens

United Network for Organ Sharing (UNOS) registry data showed that induction with any agent is better than no induction therapy at all [23].

Basiliximab or no induction

Major trials on basiliximab have proved its efficacy in preventing acute cellular rejection with maintenance of cyclosporine, steroids with or without antimetabolites [24,25]. Other trials have shown improving trends in rejection rate though not statistically significant [26]. Another retrospective study from SRTR (scientific renal transplant registry) showed small but significant reduction in acute rejection with basiliximab compared to no induction [27]. However, none of these trials showed any difference in graft survival or patient survival. One meta-analysis published in 2004, which included 14 trials enrolling 2410 patients compared basiliximab with placebo and showed reduced acute rejection rate at one year, but the incidence of graft loss was similar [28].

ATG compared to no induction

In deceased donor transplantation, two randomized control trials have shown reduced acute rejection rate with rATG. In one study (2001), combination of rATG and tacrolimus was used whilst the other study (2003) used rATG and cyclosporine. Both studies showed reduced rejection rate but with higher incidence of leucopoenia, thrombocytopenia and opportunistic infection especially cytomegalovirus (CMV). Although the incidence of acute rejection was lower in rATG group compared to placebo, there was no difference in graft or patient survival [29,30].

Meta-analysis by Liu Y which included six randomized control trials with 823 patients did not show any difference between ATG versus basiliximab in outcomes that included biopsy proven acute rejection (BPAR), graft survival and patient survival [31]. One of the drawbacks of this meta-analysis was the heterogeneous study population and it included all preparations of ATG. One of the studies included in the meta-analysis used equine ATG or basiliximab with delayed and early initiation of cyclosporine respectively, had similar rejection rate [32].In another multicenter randomized study in Europe (2002) with rATG alone or basiliximab with steroids, mycophenolate mofetil (MMF), early cyclosporine (basiliximab group) and delayed cyclosporine (rATG group), there was no difference in BPAR or renal function at one year [33]. Long term follow up at 5 years did not show any difference in outcome including incidence of CMV infection. Limitation of this study was sub optimal immunosuppression, low immunological risk group and lack of data on pre-transplant CMV seropositive status.

In a randomized study Mourad G from Europe (2004) comparing rATG and basiliximab where cyclosporine was introduced when creatinine was less than 2.7 mg/dl, and already commenced on with steroids and MMF, did not show any difference in rejection rate at one year (basiliximab 9.6%, ATG group 9.4%) [34]. There was a statistically significant increase in leucopenia (19.2% vs 51.0%, p=0.0007), CMV infection rate (21.2% vs 41.5%, p=0.025) in rATG group despite chemoprophylaxis for CMV in seropositive donor/seronegative recipient transplantation.

In another large trial (2006) involving patients at high risk for acute rejection or delayed graft function, who received renal transplant from deceased donor, induction therapy consisting of ATG as compared with basiliximab had reduced incidence and severity of acute rejection but not the incidence of delayed graft function. Positively, even at 5 year follow-up there was a decreased incidence of rejection in the rATG group [35]; however this group had higher incidence of leucopoenia although the rate of CMV infection was similar.

Alemtuzumab versus other induction drugs

In one large multicentre randomized control trial published in 2011, which compared alemtuzumab versus basiliximab (low immunological risk) and alemtuzumab versus rATG (high immunological risk), the incidence of BPAR was less in the alemtuzumab group (in low immunological risk) although it did not translate into better graft survival [36]. Alemtuzumab group had a higher incidence of late acute rejection compared to other two induction agents. A meta-analysis (2012) on alemtuzumab as induction agent which include six randomized trials with 808 patients showed reduced incidence of BPAR in the alemtuzumab group compared to other induction group (except in high risk recipients), however, it did not translate into better graft or patient survival [37]. High risk recipients as defined by panel reactive antibody (PRA) >10%, re-transplant, black race had similar BPAR in all the groups

Immunological risk

Immunological risk of a particular recipient depends upon both donor characters and recipient status. The principle of induction is to minimize the risk of rejection while keeping the risk of side effects such as cytopenia, infection and malignancy as low as possible. The choice of induction agent depends upon the immunological risk status of recipient. Table 5 shows characteristic of low and high risk groups.

Table 5: Characteristics of low and high risk groups.

Lower risk	High risk
Zero HLA match	HLA mismatch
Live donors	Younger recipient and older donor age
Caucasian ethnicity	African-American ethnicity
Low panel reactive antibody (PRA)	High PRA
Absence of donor specific antibody (DSA)	Presence of DSA
Blood group compatibility	Blood group incompatibility
Immediate graft function	Delayed graft function
Short cold ischemia time	Long cold ischemia time
First transplant	Re-transplant.

Live donors

A retrospective study compared induction versus no induction in living donor transplantation in two time periods (1998-2002) versus (2003-2008), which showed no difference in graft and patient outcome at five year follow up; however the type of induction agent was not analysed [38]. Induction therapy with different drugs has shown short term benefit in the form of reduced incidence and severity of acute rejection without any effect on long term graft and patient survival. Some studies have compared no induction with individual induction agents such as ATG, basiliximab and alemtuzumab in live kidney transplant with different results. A single centre study compared rATG with no induction control group showed superior graft and patient outcome at 5 years [39]. Similar results have been found in single centre studies in unrelated renal transplantation [40]. Other studies have found lower acute rejection rate at one year with alemtuzumab and basiliximab compared to controls with no induction [41,42].

A prospective study from Egypt (2008) showed26% reduction in incidence of acute rejection at one year with basiliximab compared to no induction with maintenance immunosuppression of steroids, cyclosporine and azathioprine [43]. Various Induction agents have been used with early corticosteroid withdrawal. A prospective multicentre randomised control trial (2010) with early corticosteroid withdrawal with ATG induction versus chronic corticosteroid therapy without induction , showed similar BPAR at 6 and 12 months in both groups, however, early corticosteroid withdrawal group had better lipid profile and less weight gain [44].

Deceased donor

Like live donor renal transplantation cadaveric renal transplantation with zero mismatches are considered low immunological risk. A review showed that in zero mismatched cadaveric renal transplantation, various induction agents (ATG, basiliximab, alemtuzumab) had lower rejection rates at 6 months post transplantation compared to no induction, although both groups had similar patient and graft survival [45].

Standard criteria donor

A secondary analysis of a randomized control trial (2006) comparing ATG with basiliximab in standard criteria deceased donor transplant showed reduced incidence of acute rejection, graft loss or death in the ATG group [46].

Delayed graft function

A prospective study in deceased donor transplantation showed that an intra-operative first dose of rATG is better than post operative ATG with respect to renal function at day 14 post transplantation. Some of the beneficial effects of intra-operative ATG could be due to prevention of acute rejection and, thereby, preventing delayed graft function [15].However, there are studies which do not support the hypothesis that ATG prevents delayed graft function [35].

Ethnicity

The African American race is at higher immunological risk of rejection when compared to Caucasian. A retrospective study in the US showed that there was no difference in outcome in terms of graft and patients survival in African American and Caucasian with ATG or Basiliximab induction. However, some other studies in Chinese patients did not show beneficial effect of basiliximab induction in preventing acute rejection [47,48].

Recipient age

In contrast to young kidney transplant recipients, elderly recipients have a high incidence of post operative complications including infection due to low immunity. A retrospective database analysis in deceased donor transplantation in elderly recipients showed that ATG was preferable in high risk recipient (PRA>20%, black race, re-transplant) with high risk donors (ECD, DCD, cold ischemia time >24 hours). ATG was also preferred in low risk recipients with high risk donors, although this study was not a randomized control trial and was blighted with multiple bias [49].

Immunosuppressant minimization

There are studies which justify the use of ATG in low immunological risk groups who have undergone early corticosteroid withdrawal. In a randomized control trial by Vanrenterghem et al. [50] ATG was shown to be effective in preventing acute rejection compared to no induction in early corticosteroid withdrawal group. Additionally, in a retrospective study of live donor recipients with early corticosteroid withdrawal, induction with r ATG was superior to no induction with respect to lower incidence of acute rejection [51].

Locally, in St John's Medical College Hospital, Bangalore, we perform live donor renal transplantation without any induction in low immunological risk group. The decision to avoid induction in low immunological risk group is driven by cost factors and absence of long term benefit in Indian population. We commence immunosuppression two days prior to the date of transplantation and the recipient receives bolus IV steroids intra-operatively followed by a tapering dose of oral steroids, tacrolimus and MMF post-op. In patients with lower risk of rejection, the avoidance of induction therapy decreases the cost of transplantation, which is the most important determining factor for opting for renal transplantation as a modality of renal replacement therapy. Our local centre protocol for induction in low immunological risk living donor renal transplant (Table 6).

Evidence for induction from Indian studies

There are limited numbers of studies from India which compare different induction regimens. Data is even more sparse when it comes to low immunological risk groups. An observational study by Gundlapalli S et al. (52) intermediate risk group with poor HLA match, compared basiliximab induction with placebo in 46 living donor renal transplant recipients with tacrolimus, MMF and steroids as the maintenance immunosuppressive regimen; there was no difference in acute rejection rate. The study concluded that

expensive induction regimen of basiliximab in the intermediate immunological risk group did not confer any added advantage to existing triple immunosuppression. The limitations of the study were lack of randomization, small number of patients and short follow up.

A study by Mahendra A et al. [53] in living donor kidney transplant recipients with long term follow up showed a reduced rejection rate with basiliximab compared to no induction; however, there was no effect on graft survival or patient survival at five years. The occurrence of infection was also higher in basiliximab group compared to placebo. Similar results have been found in other major studies elsewhere in world [28,43]. In a retrospective study that compared ATG and basiliximab in 86 living donor renal transplantation recipients, there was no difference in long-term outcomes including patient and graft survival [54]. There are no randomized control trials from India which compared various induction agents with placebo in low immunological risk groups. The long term outcome of avoiding of induction is also unknown in this population.

One of the drawbacks of avoiding induction agents in low immunological risk groups is the requirement for intensive follow up post transplantation as theoretically these patients are at higher risk of rejection. In the era of tacrolimus, MMF and steroid combination, the avoidance of induction is worth the benefit in low immunological risk groups especially in a country like India where financial and physical resources are the major limiting factors. In addition, there is a lower risk of opportunistic infection with avoidance of Induction. Treatment of opportunistic infection with antimicrobials adds to post transplantation expenditure. However, the final word on the optimal induction regimen in low immunological risk group in Indian setting is yet to be established and there is clear need for well conducted randomised trials by investigators in India.

Table 6: Transplant protocol at our local centre.

Day of transplant	Drugs used	Comments
-2 day of transplant	Start tacrolimus and MMF	Tacrolimus- 0.1mg/kg MMF- 30mg/kg in two divided doses
Transplant day	Inj methylprednisolone 1000mg No induction	
Day 1	Tab prednisolone 20 mg+ Tacrolimus+ MMF	
Day 5	Tacrolimus +MMF+ steroids	Monitor Tacrolimus level Target trough 12-15mcg/ml
4 weeks post transplant	Minimize prednisolone by tapering 2.5 mg/week + Tacrolimus +MMF	AUC for MMF is not done.
6 months	Prednisolone 5mg + Tacrolimus+ MMF	Target Tacrolimus level 8-12 mcg/ml
1 year	Prednisolone 5 mg+ Tacrolimus+ MMF	Target Tacrolimus level 5-8 mcg/ml

Conclusion

The immunological risk profile of the recipients determines the choice of induction agents. In high immunological risk status, ATG has been shown to improve graft outcomes, whereas in low immunological risk group basiliximab and ATG are equally efficacious, although with higher incidence of side effects with ATG. In low immunological risk groups the evidence supporting the use of induction drugs is rather weak, especially from India, as there no well conducted randomized studies. In addition, the infectious complications of induction regimen and cost of chemoprophylaxis with certain induction agents adds cost to existing transplant expenditure. In the background of no proven long term benefit of using induction agents in recipients with low immunological risk in Indian population, the avoidance of induction agents may be a good option in order to save the cost and potential morbidity.

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Citation: Shenoy P, Bridson JM, Halawa A, Sharma A (2016) Induction Agent in Low Immunological Risk; the Indian Scenario. Urol Nephrol Open Access J 3(6): 00106. DOI: 10.15406/unoaj.2016.03.00106

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Citation: Shenoy P, Bridson JM, Halawa A, Sharma A (2016) Induction Agent in Low Immunological Risk; the Indian Scenario. Urol Nephrol Open Access J 3(6): 00106. DOI: 10.15406/unoaj.2016.03.00106

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Citation: Shenoy P, Bridson JM, Halawa A, Sharma A (2016) Induction Agent in Low Immunological Risk; the Indian Scenario. Urol Nephrol Open Access J 3(6): 00106. DOI: 10.15406/unoaj.2016.03.00106