

Review Article

Induction with Thymoglobulin in High-Risk Renal Transplant Patients; Beauty and the Beast

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Abstract

Renal transplantation remains the treatment of choice in renal failure patients, one of the major challenges is to promote acceptance of the newly transplanted graft by the host immune system. Therefore, induction protocols were adopted to achieve this objective. The aim of induction immunosuppression is to reduce the risk of acute rejection and delayed graft function (DGF).

The optimum induction protocol remains uncertain. However, induction regimens utilizing biological antibodies proved to be not only safe and effective, but also they allow better patient and graft survival.

Biological antibodies can be categorized into depletive (e.g. Antithymocyte globulin (ATG) and Alemtuzumab) and non-depletive antibodies (e.g. Basiliximab). Their use in the perioperative period has the advantage of lowering the doses of maintenance immune suppression, and even allows complete withdrawal or avoidance of some of these agents and their associated side effects. It also draws great attention in the promising strategies to induce tolerance of the host immune system to the transplanted graft, which if therapeutically achieved, will be considered a revolutionary step in the transplantation immunology.

The aim of our review is to focus on ATG, which is considered one of the effective induction agents, demonstrating its established and potential uses in respect of induction immune suppression.

Keywords: Transplantation; ATG; Induction and Immune Suppression

Introduction

The main aim of a transplant physician is to provide the optimum management for the transplant recipient in order to improve the long-term patient and graft survival [1]. Acute rejection and delayed graft function (DGF) are important factors that affect long-term graft survival [2].

The risk of acute rejection is highest in the early post-transplant period, so induction therapy was developed to decrease the incidence of acute rejection, this will allow the

use of lower doses of maintenance immune suppression and even may assist in the development of tolerance in solid organ transplantation [3].

Up till now, there is controversy regarding the optimum induction immune suppression protocol [4]. Different protocols exist based on local expertise and available resources; but generally it can be categorized into two main groups as shown in Table 1.

Although the term induction therapy can be applied to any

immune suppression drugs that are given in the perioperative period, yet it has been commonly used to describe the use of biologic antibodies against different immune system targets in the immediate perioperative period [5]. A large number of randomized controlled studies and meta-analyses have shown that using biologic antibodies in the induction of immune suppression was superior to the use of conventional immune suppression drugs alone, as it offers better graft survival and lower incidence of acute rejection [6].

Delayed graft function (DGF) is a clinical diagnosis that describes the failure of the renal allograft to function immediately post-transplantation, development of DGF is associated with recipient factors like male gender, black race, prolonged waiting time on dialysis and the degree of HLA mismatch [1]. Donor factors may also contribute to the development of DGF such as prolonged warm and cold ischaemia time, an old age donor and use of Expanded Criteria Donors (ECD) [1].

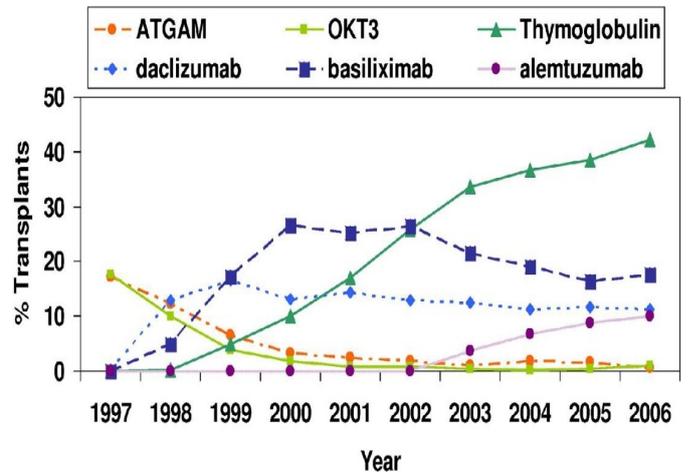


Figure 1. The Use of Induction Antibodies in The United States From 1997 To 2006 [5].

	Conventional drugs induction	Antibody induction
Drugs used in the protocol	Initial high doses of CNI + antimetabolite + steroids.	Depleting or non-depleting biological antibodies + lower doses of conventional drugs.
Indications	Low immunological risk transplantation	High immunological risk transplantation.
Advantages	- Cheap. - Less risk of infection. - Easier to monitor.	- Potent and effective immune-suppression. - Allow lower doses of maintenance immune-suppression (and even avoidance of some of them)
Disadvantages	- Not suitable in high-risk cases. - Higher doses of drugs mean more adverse effects (e.g. DGF with CNI).	- Expensive. - Higher risk of infection. - Complex prescription and monitoring.

Table 1. Induction Immunosuppressive Strategies in Renal Transplantation.

Induction therapy was proved to be effective not only in reducing the acute rejection rate, but also in reducing the incidence of (DGF) [2]. Reports from the United States has documented that 70% of patients had received one of the induction antibodies as illustrated in figure 1 [5].

In 2009, Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group has suggested using one of the lymphocytes depleting agents in high-risk transplantation [7]. High immunologic risk of acute rejection can be anticipated in the presence of one or more of the following factors (7):

- 1) High panel reactive antibody (PRA).
- 2) Increased number of HLA mismatch.
- 3) Old aged donor.
- 4) Afro-American ethnicity.
- 5) Prolonged cold ischemia time.
- 6) The presence of donor-specific antibody (DSA).
- 7) ABO-incompatible transplantation.

When applying all the data mentioned above to my local transplantation environment, two points should be considered:

First: we are only dealing with living kidney transplantation (deceased organ transplantation is legally prohibited in my country to the moment).

Second: with resource-limited setting, the financial cost is a key consideration.

Our local protocol divides the patients according to their immunological risk, i.e., into high and low-risk groups based on KDIGO criteria [7]. The high-risk groups are eligible for induction with biological antibodies, while the low-risk groups receive high-dose conventional immune suppression drugs as induction.

Antibody Induction in High-Risk Renal Transplant Patients

Antibodies used in induction protocols, are either monoclonal (e.g. basiliximab), which is targeted to a single cell surface receptor as illustrated in figure 2 [8], or polyclonal ATG, which is directed against many different cell receptors (e.g. CD3/TCR, CD25, CD28, CD40, CD80, and CD86), adhesion molecules and

cell trafficking molecules (e.g. CD11a/CD18 (LFA-1), CD54 (ICAM-1), and CD195 (CCR5)), and other pathways mediators like CD2 and CD45 [4, 5].

Another common classification of biological antibodies is to divide them into depleting and non-depleting antibodies as summarized in Table 2 [8].

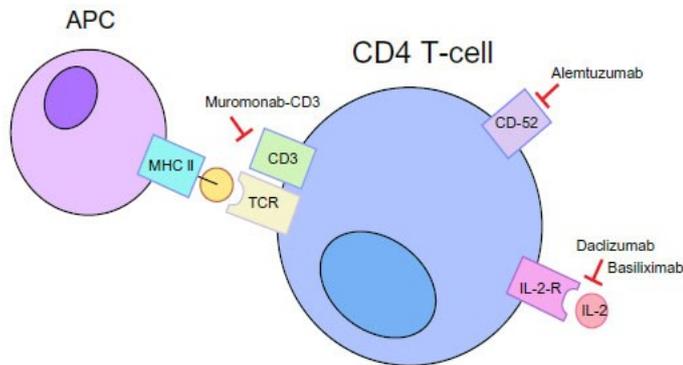


Figure 2. Monoclonal Induction Agents and Cellular Binding Sites [8].

OKT3 (Anti-CD3 antibody) is a chimeric depletive monoclonal antibody that was used previously. It is non-humanized mouse antibody with serious side effects that was withdrawn by the manufacturer due to declining sales [1].

ATG is a depleting agent with profound immune suppressant activity. It contains antibodies that will not only affect T-cells but also it will have an impact on a broad range of other immune system cells e.g. naive and activated B cells together with bone marrow resident plasma cells [9]. It is prepared by immunization of an animal with human thymocytes. The animal is either rabbit (in this case it will be named rATG or Thymoglobulin), or horse (called ATGAM) [10]

In our centre, Thymoglobulin is used as the induction agent in high-risk transplantation, and therefore we will discuss this protocol in more detail here in view of our experience.

Thymoglobulin is a potent agent that is useful in preventing ischemia-reperfusion injury.

Agent	Alternative name(s)	Drug class	Proposed mechanism(s) of action	Serious adverse effects
Lymphocyte-depleting				
Anti-thymocyte globulin, rabbit	rATG, Thymoglobulin®	Chimeric (rabbit) polyclonal antibodies	Exact mechanisms unknown; broadly targets and eliminates pre-activated, non-cycling memory lymphocytes; alters T-lymphocyte activation, homing, and cytotoxic function	Cytokine release syndrome (fever, shivering, myalgia, headache), hypertension, anaemia, leukopenia, thrombocytopenia, increased risk of infection
Anti-thymocyte globulin, equine	eATG, Atgam®	Chimeric (equine) polyclonal antibodies		
Alemtuzumab	Campath®	Humanized monoclonal antibody against CD52	Targets most mature some immature lymphocytes; exact mechanism unknown, but may cause antibody-dependent lysis of cells following cell surface binding	
Muromonab-CD3	OKT3, Orthoclone®	Chimeric (murine) monoclonal antibody against CD3	Broadly targets all circulating T-lymphocytes; promotes antibody-mediated activation of complement and apoptosis of T-lymphocytes	
Lymphocyte non-depleting				
Daclizumab	Zenapax®	Chimeric (murine) monoclonal antibody against CD25 IL-2 receptor	Specifically, targets T cells that have been activated by an MHC-antigen stimulus; inhibits T-lymphocyte activity	Cytokine release syndrome (fever, shivering, myalgia, headache), hypertension, anemia, leukopenia, thrombocytopenia, increased risk of infection
Basiliximab	Simulect®			

Table 2. Lymphocyte-Depleting and Non-Depleting Induction Agents [8].

It is thought to induce T-cell depletion through variable mechanisms, including complement dependant cytotoxicity, antibody dependant cell mediated cytotoxicity, opsonisation and phagocytosis by macrophages and induction of apoptosis [1]. Thymoglobulin is also thought to selectively increase expansion of Treg cells (CD4+CD25+Foxp3+ T cells), which attracts great attention due to its role in long-term immunomodulation [11].

This potent drug has well-recognized adverse effects that are mostly due to the animal origin of antithymocyte immunoglobulin, it ranges from serious events like anaphylaxis, cytokine release syndrome and serum sickness, to more tolerable leukopenia, thrombocytopenia, flu-like symptoms and increased risk of infection. It is also accused for the increased incidence of post-transplant lymphoproliferative disease (PTLD) [5, 12]. That is why it is a common practice to use corticosteroids, diphenhydramine, and acetaminophen just before Thymoglobulin administration [8]. It is worth to mention that leukopenia and thrombocytopenia can be aggravated by the concomitant use of some medications like mycophenolate mofetil and valganciclovir, which are commonly used in transplant recipients. Daily check of the white blood cell and platelet counts is advisable [8].

Comparing Thymoglobulin versus ATGAM

Brennan et al. (1999) had a leading study that demonstrates lower incidence of acute rejection (4.2% versus 25%; $p = 0.014$) and better one-year graft survival with Thymoglobulin (98% versus 83%; $p = 0.020$). Thymoglobulin group had more leukopenia, yet they had a lower incidence of CMV disease (10% versus 33%; $p = 0.025$). There were no differences in patient survival and graft function at 12 months; none of both groups' patients develop PTLD [13]. At ten year follow up of the same group, the incidence of acute rejection was lower in Thymoglobulin group (11% vs. 42%; $p = 0.004$), while patient and graft survival were similar in both groups. It is worth to mention here that mean serum creatinine was higher (1.7 +/- 0.5 mg/dL vs. 1.2 +/- 0.3 mg/dL; $P = 0.003$) and eGFR was lower (49 +/- 22 mL/min vs. 65 +/- 19 mL/min; $P = 0.065$) in the Thymoglobulin group [14].

Based on the above data, we conclude that the use of Thymoglobulin as the antithymocyte globulin of choice is justifiable and appropriate.

Comparing Thymoglobulin with Basiliximab

A large, prospective, randomized, multicentre study had compared 141 patients who received induction therapy with Thymoglobulin (1.5 mg/kg daily for five days starting from the day of transplantation), against 137 patients who received induction with basiliximab (20 mg/day on Days 0 and 4) [15]. Both groups received cyclosporine, Mycophenolate Mofetil, and prednisone as maintenance immunosuppression.

At one-year follow-up, there was no significant difference in patient and graft survival, however, Thymoglobulin group had lower incidence of acute rejection (15.6% versus 25.5%, $P = 0.02$) and cytomegalovirus (CMV) disease (7.8% versus 17.5%, $P = 0.02$), while infectious complications were lower in basiliximab group (75.2% versus 85.8%; $p = 0.03$) [16].

Moreover, after five years of follow-up, Thymoglobulin group had maintained efficacy in the form of a lower incidence (37% versus 51%, $P = 0.04$) of the composite end point (development of acute rejection, graft loss or death) [17].

On the other hand, a meta-analysis of 18 randomised controlled trials (RCTs) (1844 participants) that compared IL-2 receptor antibodies versus ATG found that there was no difference in graft survival or clinically diagnosed acute rejection between both induction modalities at any time point, however, ATG had a lower incidence of biopsy-proven acute rejection (BPAR) at one year (eight studies: RR 1.30 95% CI 1.01 to 1.67), but at the cost of increased adverse effects including 75% increase in malignancy (7 studies: RR 0.25 95% CI 0.07–0.87), 32% increase in CMV disease (13 studies: RR 0.68 95% CI 0.50–0.93). ATG patients had significantly more adverse reactions to drug administration like fever, cytokine release syndrome and more leukopenia [18].

Brokhof et al. (2014) included in their study 114 consecutive moderately sensitized recipients, who had positive donor-specific antibodies (DSAs), but with negative flow crossmatch at the time of transplantation. Patients were divided into two groups, 85 patients had induction therapy with ATG while the other 29 received basiliximab. They concluded that induction with ATG was not only associated with the lower incidence of de novo donor-specific antibodies, but it also associated with a decrease in the antibody-mediated rejection when compared with basiliximab at three years follow-up [19].

Considering the above-mentioned comparable studies, Thymoglobulin remains the best choice to be used whenever high-risk kidney transplantation is planned in my local hospital.

Comparing Thymoglobulin to Alemtuzumab:

Alemtuzumab is a humanized monoclonal antibody targeting CD52, which is present on almost all B and T lymphocytes, as well as natural killer cells, macrophages and some granulocytes [20, 21]. Alemtuzumab induces marked lymphocyte depletion via antibody dependant cell lysis, an effect that will persist for several months [22, 23].

Farney and his colleagues in 2009 studied the efficacy of Alemtuzumab in comparison to Thymoglobulin as an induction agent [24]. 109 patients received Thymoglobulin as an induction before kidney and pancreas transplantation, were compared to 113 patients who received Alemtuzumab,

immunologic risks were similar between the two groups. With a median follow-up of 2 years, patients and graft survival were similar for both groups as well as incidence of infection and malignancy, but the incidence of BPAR was higher in Thymoglobulin group (26% versus 14%; $p = 0.02$) [24].

In another prospective study, patients were randomly assigned to receive Alemtuzumab, basiliximab or Thymoglobulin according to their immunological risk [25].

In the high-risk group, there was no difference in the incidence of acute rejection between patients who received Alemtuzumab and their comparative group who received Thymoglobulin after a follow-up for three years. While in the low-risk group, there was a therapeutic advantage of Alemtuzumab over basiliximab in the form of lower BPAR at three years follow-up (10% vs. 22%, $P=0.003$) [25].

Opelz et al. (2016) compared the efficacy of antibody induction therapy (namely Thymoglobulin and interleukin-2 receptor antagonist (IL-2RA) in high and low-risk kidney transplantation. They analysed data of 38,311 first deceased donor kidney transplants that were performed between 2004 - 2013. The conclusion of this analysis showed a clear benefit of antibody induction in high-risk transplant, but it fails to prove statistical benefit of this strategy in low-risk transplantation. On the contrary, the hospitalization secondary to infection was increased with both induction agents [26].

The studies mentioned above are different from our local practice as they used antibody induction not only in high-risk scenarios but also in low-risk situations. Do we still need to use antibody induction in low immunological risk patients? Will it be cost effective giving the low immunological risk and the side effect of the Thymoglobulin? We strongly believe that the opposite is true, where Basiliximab is ideal for those with low immunological risk even so it did not improve graft survival in Tacrolimus- based immunosuppression era [27].

Role of Thymoglobulin in Tolerance Induction Protocol:

Tolerance can be defined as a well-functioning graft without any histological signs of rejection, while the recipient (who is immune competent) is not on any immunosuppression drugs for at least one year [28].

Stanford University had a leading study about induction of tolerance using post-transplant conditioning. The study included 38 kidney transplant candidates who had living donors. The patients were given combined kidney and enriched CD34+ hematopoietic cell transplants to achieve mixed chimerism as illustrated in figure 3 [28]. The recipients received induction therapy in the form of Thymoglobulin (1.5 mg/kg/day) for five days starting intraoperatively and total lymphoid irradiation for ten days [29]. About 75% of HLA matched recipients achieved complete withdrawal of immune suppression medications for up to 5 years without evidence of

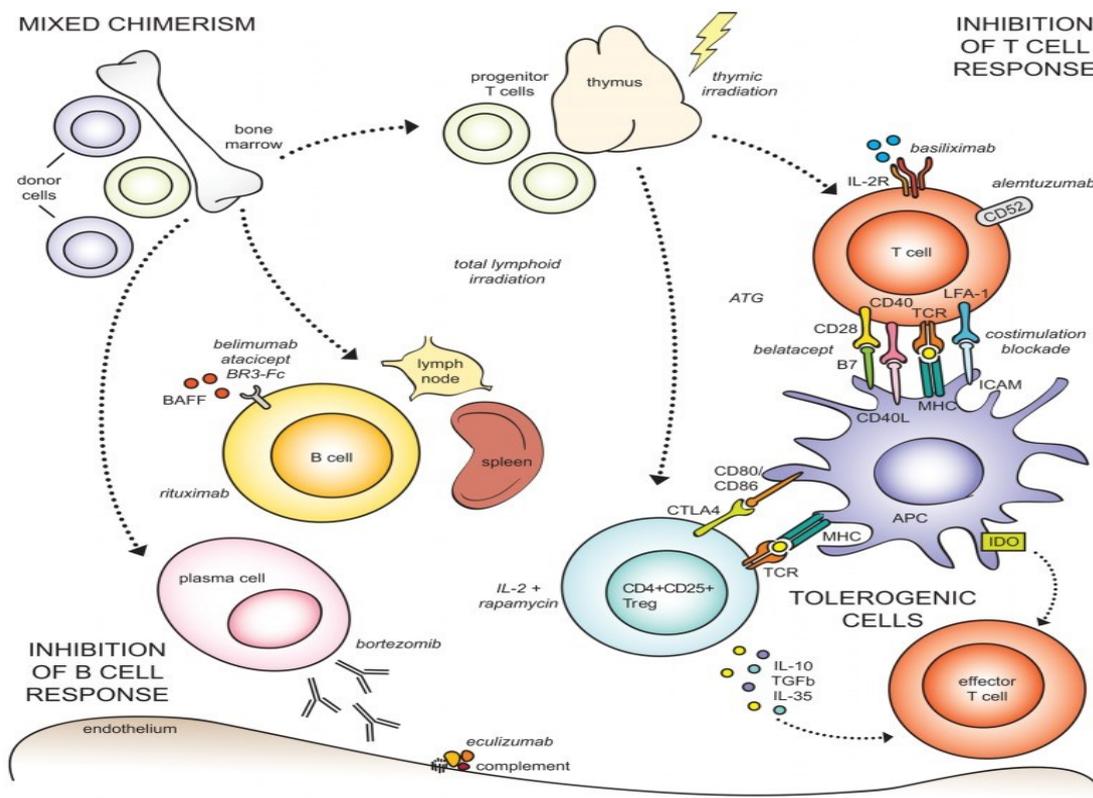


Figure 3. Diagram Of Achieving Tolerance By Eliminating Alloreactive Immune Cells And Potentiating Mixed Chimerism [28].

rejection or recurrence of renal disease, none of the patients suffered from graft versus host disease or kidney graft loss [29].

Dosing Regimen of Thymoglobulin:

Pennington et al. (2015) studied a total number of 261 adult kidney transplant recipients who were divided into two groups based on the dose of Thymoglobulin given during induction; all recipients were maintained on tacrolimus, mycophenolate, and prednisone. The first group received a cumulative Thymoglobulin at the dose of 5 mg/kg or higher (5.2 ± 0.2 mg/kg, $n = 138$) while the other group received a cumulative dose lower than 5 mg/kg (4.5 ± 0.6 mg/kg, $n = 123$) [30]. The incidence of BPAR was similar in both groups (8.7% for the first group versus 8.9% in the second group, $P = 0.944$). Patient survival, graft survival and graft function were similar at 12 months of follow-up. They concluded that lower cumulative dose of Thymoglobulin provides a chance for cost saving without compromising the efficacy of the drug [30].

Agha et al. (2002) published a prospective, non-randomized trial in which he compared the results of 40 patients received Thymoglobulin induction for 3 days (3 mg/kg intraoperatively, followed by 1.5 mg/kg on days 1 and 2) with a historical group of 48 patients that received 7 days of Thymoglobulin (1.5 mg/kg intraoperatively, then daily for six days) [31]. At one-year evaluation, there were no differences in incidence of acute rejection, patient and graft survival were similar in both groups. The duration of hospitalization post-transplantation was shorter in the 3 days' group (6.1 versus 8 days), and they have also more profound lymphocytic depletion that persists for longer duration as compared to the 7 days' group [31].

There are several other studies that analysed different dosing strategies of Thymoglobulin (from 1 to 6 mg/kg per dose) and for various durations (ranged from 1 to 10 days), however, the more typical regimen is 1.5 mg/kg for three to five days [4].

Our local protocol suggests receiving Thymoglobulin at a dose of 1.5 mg/kg for three to five days, which is in agreement with the international practice.

Thymoglobulin in Special Populations:

Recipient obesity: obesity is a challenging problem in renal transplant recipients that is associated with increased morbidity, mortality and graft loss [32]. In spite of these facts, kidney transplantation offers a survival benefit as compared to dialysis in obese patients [33]. The obesity prevalence increased in the United States renal failure patients who started dialysis, most probably secondary to improved survival and sedentary life [32, 34]. This will be reflected in rising numbers of obese patients in transplantation waiting list.

Patel et al. (2011) studied the long-term outcome of low dose

Thymoglobulin versus basiliximab induction in obese (body mass index (BMI) greater than 30) and non-obese patients. At a mean follow-up of 47.4 ± 10 months, graft survival was better in Thymoglobulin group both in obese (90.3% versus 63.6%, $P < .05$) and non-obese patients (88.7% versus 68.2%, $P < .05$). There was no difference in patient and graft survival between obese and non-obese recipients who received Thymoglobulin [32].

Paediatric recipients: Although data from adult transplantation studies are considered during the management of paediatric patients, immunosuppression usually needs to be modified according to their effect on growth and development of the patient [35].

Khositseth et al. (2005) presented a retrospective single-centre study that compared Thymoglobulin with ATGAM, patient and graft survival were similar between both groups, but the incidence of acute rejection was higher in ATGAM group [36]. Another single centre study concluded that Thymoglobulin induction and steroid minimization results in favourable linear growth, stable graft function, stable or improved cardiovascular risk and normal bone density in paediatric recipients, there were no clinical episodes of EBV or CMV infection among 44 patients included in the study [37]. These results came in agreement with another two small studies, which utilized induction with Thymoglobulin to allow steroid free maintenance immune suppression. The 2 studies reported acute rejection, patient and graft survival rates comparable to steroid based maintenance protocols [38, 39].

Elderly recipients: kidney transplant recipients aged > 60 years are exposed to higher risk of post-operative complications [40, 41]. They are more likely to have pre-existing co-morbid conditions, which significantly increase the risk of morbidity and mortality after transplantation [40].

Laftavi et al. (2011) studied the effect of low-dose induction therapy with Thymoglobulin in 45 patients older than 65 years, as compared with another 45 patients younger than 65 years. The dose of Thymoglobulin was 2.96 ± 1.29 mg/kg in the older age group versus 3.2 ± 2.11 mg/kg in the younger group. All patients have received maintenance immune suppression in the form of a calcineurin inhibitor (CNI), mycophenolic acid, and low-dose prednisolone (5 mg/d) (41). They concluded that this induction protocol was safe and effective in this age group with a three-year patient and graft survival comparable to that observed in younger age recipients [41].

We are currently not performing kidney transplantation for these special subsets of patients, so we do not have the experience to urge against these trials.

Hepatitis C virus-seropositive (HCV+) recipients: Hepatitis C virus prevalence is higher in end-stage renal disease patients on maintenance dialysis [42]. HCV+ transplant recipients

have improved survival in comparison to those who remained on dialysis [43, 44], but when compared to HCV-negative recipients there is increased risk of patient death (HR = 1.30, 95% CI 1.20–1.41, $P < 0.0001$) and this risk decreases with older recipients [42].

Among HVC+ recipients, induction with biological antibodies was associated with decreased hazard ratio (HR) for patient death (HR = 0.75, 95% CI 0.61–0.90, $P = 0.003$), an effect that was also noticed in patients treated with mycophenolate mofetil (MMF) (HR = 0.77, 95% CI 0.64–0.92, $P = 0.005$) [42].

Human immunodeficiency virus (HIV) positive recipients: ESRD patients with HIV infection were once prohibited from receiving kidney transplant secondary to limited life expectancy. The development of highly active antiretroviral therapy (HAART) had markedly improved the survival of HIV-infected patients, and this led to include patients with well-controlled HIV infection in the transplantation waiting list [8]. The use of Thymoglobulin in this special population was not associated with increased risk of progression to acquired immunodeficiency syndrome (AIDS) or death [45]. However, it was associated with marked CD4+ T-cell and total lymphocyte depletion, this increased risk of severe infection requiring hospitalization [45]. In light of these data, it is advisable to restrict the use of Thymoglobulin to patients at high immunological risk of rejection, with close monitoring of lymphocytic count [8].

Our Protocol for Induction Therapy In High-Risk Cases:

The immune suppression is commenced at 6.0 AM on the day of transplantation by giving the patient 500 mg intravenous (IV) prednisolone, then the intraoperative infusion of 1.5 mg/kg Thymoglobulin.

Thymoglobulin will be given daily for another four days. Oral immunosuppression will start from day 1 (second day post-operative). We start 0.05 mg/kg Tacrolimus twice daily adjusted to achieve a trough level of 7 to 10 ng/ml, 500 mg (MMF) twice daily and oral prednisolone 1 mg/kg once daily (maximum 60 mg per day) that will be decreased by 5 mg every 3 days till we reach 20 mg daily. After that, tapering will be more slowly over weeks to reach 10 mg final maintenance steroid dose. In the first few days post-surgery, we hold Thymoglobulin and MMF if the white blood cell (WBC) count drops to less than 2000/microL or the platelet count decreases to less than 75,000/microL. And they are not restored till WBC count became more than 3000/microL and platelet count more than 100,000/microL.

After careful review of literature, we realized that there are no universal dosing recommendations for Thymoglobulin, yet most of the trials showed that low dose for 3 – 7 days was sufficient to achieve acceptable results, and this matches

our local practice. However, unlike our centre, they used the potent lymphocytic depleting effect and subsequent immune suppression as a tool for minimization or even avoidance of other maintenance immune suppressant (e.g. steroid avoidance in children to avoid their effect on growth and development and CNI minimization and avoidance to prevent their nephrotoxic complication). These protocols are well supported by well-organized clinical trials, which were conducted by different transplantation centres across the world.

Conclusions

1. There is no ideal induction protocol. Rather there are different approaches based on risk stratification of each patient.
2. Antibody induction therapy proved to be safe and efficient, with an excellent patient and graft survival, especially in high-risk transplantation.
3. Thymoglobulin (rATG) is more potent and provide a therapeutic advantage over other biological antibodies used in induction therapy, yet it's optimum dose and regimen is uncertain.
4. Thymoglobulin has a markedly heterogeneous cell receptors target antigens, which explain the potent lymphocytic depletive action of this agent, this may be used in the induction of tolerance protocols in the future.

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