Thymoglobulin and Its Use in Renal Transplantation: A Review

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Key Words

Kidney failure · Transplantation · Rejection · Immunosuppression

Abstract

Thymoglobulin (Thymoglobulin®; Genzyme, Cambridge, Mass., USA) is a polyclonal antibody which has been used in the field of transplantation over the last four decades. With an initial hesitancy, it is widely used now in the prevention and treatment of rejection following renal transplantation. Thymoglobulin's lack of nephrotoxic properties (unlike calcineurin inhibitors) may potentiate it to be a very useful induction therapy during the early days following transplantation, particularly in a donation after circulatory death programme. More recently its role in conjunction with inhibitors of terminal complement activation has been shown to be beneficial in cross-match-positive transplantation. This review article consolidates up-to-date available evidence to address the therapeutic role of thymoglobulin in immunological tolerance, ischemia perfusion, live donor transplantation, delayed graft function, prevention and treatment of rejection, graft survival and post-transplant lymphoproliferative disorder following renal transplantation.

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Background

Thymoglobulin (Thymoglobulin®; Genzyme, Cambridge, Mass., USA) is a purified polyclonal immunoglobulin used for prevention and treatment of acute rejection (AR) following renal transplantation.

Thymoglobulin is mostly used for treating vascular, steroid-resistant and antibody-mediated rejection. The antirejection efficacy of thymoglobulin was first established in 1999 when compared with equine antithymocyte globulin (eATG) (Pharmacia-Upjohn, Kalamazoo, Mich., USA) [1], and further supported by other studies [2–4]. The history of antilymphoid preparations started in 1899 with Metchnikoff [5]. In 1963, the role of antilymphocyte serum was tested in animals which produced lymphopenia and this led to a new strategy in managing some of the immunological aspects of transplantation [6].

The antilymphocyte serum was first used in human renal transplantation in 1965 [7] and later its use confirmed as an adjuvant immunosuppressant. In 1971, Taylor et al. [8] showed the beneficial use of eATG in a multicentre randomised controlled trial (RCT), but following the discovery of calcineurin inhibitors, a combination of ALG, azathioprine and prednisolone failed to show any advantages over cyclosporine [9]. However, because of

nephrotoxicity of cyclosporine, some centres used ALG in the early post-operative period and subsequently added cyclosporine A to the immunosuppressant regimen. In 1980, the use of eATG in steroid-resistant allograft rejection was established [10].

Thymoglobulin is prepared by immunizing pathogen-free rabbits with a cell suspension of human thymic tissue (thymocytes). After immunisation, the serum is harvested from rabbits and immunoglobulins against thymocytes are isolated and subjected to a number of purification processes [3, 11, 12]. Samples from more than 26,000 immunised rabbits are pooled to achieve a high level of batch-to-batch consistency [11, 13]. Since 1984, thymoglobulin has been used effectively in organ transplantation for the prevention and treatment of AR [14].

Mechanism of Action

The mechanism of polyclonal antilymphocyte preparations on immune responses is still not fully understood. T-cell depletion constitutes the primary mechanism, though other mechanisms, such as modulation of cell surface antigens, emerge as other possible major effectors in the immunological milieu [15].

Thymoglobulin induces lymphocyte depletion in the peripheral blood by complement-dependent cell lysis [16]. Again, this is not the only mechanism as a significant percentage of lymphocyte depletion can be antibody-mediated cytotoxicity and activation-induced cell death [16]. A lower concentration of thymoglobulin in the range of 0.1–1 µg/ml has been shown to induce lysis of preactivated T cells; at a higher concentration (10–100 µg/ml) it triggers CD178 (CD95-L) expression by resting T cells and apoptosis of preactivated T cells through pathways mostly involving Fas/Fas-L interactions [16, 17].

Lymphocyte depletion occurs rapidly after intravenous administration [1, 3] and recovery of peripheral T-cell counts occur gradually after cessation of thymoglobulin treatment. About 40% patients treated with thymoglobulin (mean of 6 doses at 1.5 mg/kg/day) recover more than 50% of initial lymphocyte count at 3 months [1].

In a series of experiments using cynomolgus monkeys, administration of rabbit ATG (rATG) at doses ranging from 1 to 20 mg/kg was shown to induce transient dose-dependent depletion of CD2⁺, CD3⁺, CD4⁺, CD8⁺, CD20⁺, and CD56⁺ lymphocyte subsets in peripheral blood. It depletes T cells not only in the periphery but also in secondary lymphoid tissues where the vast majority of T cells reside and antigen presentation occurs. Notably,

no lymphocyte depletion was observed in the thymus at any dosing level [18].

Treatment with rATG down-modulates the expression of several molecules that control T-cell activation, including the T-cell receptor (TCR)/CD3 complex, CD2, CD4, CD5, CD6, and CD8 [18]. Functional antibodies in rATG down-regulate the cell surface expression of a number of integrins and intercellular adhesion molecules (ICAMs) that facilitate leukocyte adhesion to the endothelium [17]. Reperfusion in the presence of rATG thus markedly reduced the rolling of leukocytes and almost completely inhibited the adhesion of leukocytes to the endothelium in a primate model [19].

B-Cell Depletion

rATG has been shown to strongly induce apoptosis *in vitro* against naive, activated B cells and bone marrow resident plasma cells at clinically relevant concentrations (1–100 ng/ml). rATG is thought to bind with numerous B-cell surface proteins and it is this cross-linking of CD30, CD38, CD95, CD80, and HLA-DR that likely accounts for this activity. Fab2 fragments of rATG showed 90% of the activity of the intact molecule, suggesting participation of the Fc fragment. Inhibition of caspase- and cathepsin-dependent apoptotic pathways partially inhibits rATG-induced B-cell apoptosis [20, 21].

Plasma Cell Depletion

rATG contains antibodies which can bind syndecan (CD138), a plasma-cell-specific molecule [21], although *in vivo* ATG treatment is not associated with a reduction in either splenic or bone marrow plasma cells. Clinical studies suggest that rATG may however reduce the risk of AMR in patients with preformed donor-specific antibody [22], presumably by removing T-cell help for alloreactive B cells and via B-cell depletion due to antibodies which directly bind B cells [21]. Perry et al. [23] have shown that *in vitro* rATG failed to inhibit alloantibody production by plasma cells.

Mohty [24] has shown diverse effects of ATG on the immune system; in addition to T-cell depletion, it also induced apoptosis in B-cell lineages, interference with dendritic cell functional properties, and leads to induction of regulatory T and natural killer T cells.

Interestingly, Gloor et al. [25] from Mayo Clinic showed that *in vivo* treated sera from ATG-treated patients produced positive test results for T-cell complement-dependent cytotoxicity and T- and B-cell flow cytometric (FXM), while the B-cell complement-dependent cytotoxicity cross-match remained negative. Solid-phase

assays HLA class I and II assays based on antigen-coated microspheres and enzyme-linked immunosorbent assay (ELISA) were minimally affected using in vivo treated sera. After ATG extraction, all tests became negative.

The complex and prolonged immunomodulation induced by ATG contributes to the efficacy of this agent in solid organ transplantation [26]. On assessing leukocyte adhesion by intravital microscope in an ischemia-reperfusion non-human primate model, polyclonal rATGs inhibit early leukocyte interactions with vascular endothelium, almost completely inhibiting the adhesion phenomenon in capillaries which was not seen with the anti-interleukin (IL)-2 receptor monoclonal antibodies [27].

Objectives

This review is aimed to assess and construct an evidence-based descriptive review document about thymoglobulin use in renal transplantation. It thus aims to address its role in (1) immunological tolerance; (2) ischemia reperfusion injury; (3) delayed graft function; (4) prevention and treatment of acute allograft rejection; (5) live donor transplantation; (6) graft survival and patient survival, and (7) post-transplant lymphoproliferative disorder.

Search Strategy

MEDLINE (PubMed 1966–2012), The Cochrane Central Register of Controlled Trials, EMBASE (1974–2012), the database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment (HTA) database, and by contacting manufacturers to identify relevant studies, randomised trials, meta-analysis and case series, all related reference articles in English literature were included and reviewed (see PRISMA flow diagram in fig. 1). Studies involving combined renal transplantation were excluded.

Role of Thymoglobulin on Immunological Tolerance

The regulatory T cells (Treg), a specialised subset of T cells shown to play an important role in modulating the immune response to alloantigens and in maintaining self-tolerance [28, 29], have been identified in patients with stable renal transplant where they may function to maintain the hyporesponsiveness to alloantigen [30]. Thymo-

globulin has been shown to cause significant and sustained expansion of Treg in vitro [31]. Lopez et al. [32] demonstrated that thymoglobulin expands the CD4⁺, CD25⁺, forkhead box p3 (Foxp3⁺) Treg population in a dose-dependent manner, primarily by converting CD4⁺, CD25⁺ cells into functionally immunosuppressive CD4⁺, CD25⁺ cells. More importantly, the CD4⁺, CD25^{high} Foxp3⁺ Treg cells generated by thymoglobulin were shown to suppress a direct alloimmune response in a mixed lymphocyte reaction, but did not suppress the memory response to recall antigens. LaCorcia et al. [33] showed that clinically relevant doses of thymoglobulin (in vitro) increase functionally immunosuppressive CD4⁺, CD25^{high} Foxp3⁺ Treg cells in peripheral blood. Thymoglobulin also effectively inhibits CXCR4-mediated chemotaxis of T cells. All these effects in theory may contribute to durable T-cell anergy and allograft survival.

Recently it has been shown that thymoglobulin can induce B-cell apoptosis on an in vitro model [21]. The recovery of the functional memory of T cells, considered as a major barrier to the establishment of transplantation tolerance, has been documented after lymphocyte depletion with polyclonal or monoclonal antibody treatment in clinical transplantation [34, 35]. However, previous in vivo studies have shown that the transplant tolerance can be induced by polyclonal antibody therapy [36, 37]. rATG in combination with specific donor bone marrow infusion with rapamycin has been shown to be effective in inducing transplant tolerance in major histocompatibility complex mismatched murine skin allograft models [37, 38]. A recent in vitro study [39] showed that thymoglobulin-pretreated CD4⁺ cells demonstrated up-regulation of gene transcripts for CTLA-4, OX40, Foxp3, CD25, interferon- γ (IFN- γ), IL-10 and IL-2. Fluorescence-activated cell scanning analysis demonstrated that CD4⁺ cells pretreated with thymoglobulin up-regulated CD25 expression on their surface, and the surface expression of CTLA-4 and OX40 and the expression of intracellular Foxp3 were observed in these CD4⁺CD25⁺ cells. The mixed lymphocyte reaction demonstrated that thymoglobulin-pretreated cells partially inhibited proliferation of untreated autologous CD4⁺ cells in response to allogenic cells. The lymphocyte proliferation of allogenic mixed lymphocyte reaction was also partially blocked in the presence of supernatants from cultures of thymoglobulin-pretreated CD4⁺ cells. This demonstrates that the unique effects of thymoglobulin in modulating CD4⁺ cells may be an important mechanism for its action in inducing immunosuppression and transplant tolerance.

Fig. 1. PRISMA flow diagram.

Complication Profile of Thymoglobulin

Thymoglobulin can cause acute and delayed reactions. Acute reaction will present as cytokine release syndrome which is characterised by anaphylaxis, fever, chills/rigors, dyspnoea, nausea/vomiting, diarrhoea, hypotension or hypertension, malaise, rash, and/or headache which usually can be managed by stopping infusion and epinephrine. Severe reaction includes cardiorespiratory dysfunction including hypotension, pulmonary oedema, myocardial infarction, tachycardia and rarely death [40]. Thymoglobulin is not specific for T cells but contains antibodies directed against different blood cell types (T cells > B cells; NK cells > monocytes; neutrophils > platelets > erythrocytes) [18, 41]. Because of the presence of cross-reacting antibodies against non-lymphoid cells, haemolytic anaemia, thrombosis, thrombocytopenia and neutropenia can occur [41].

Delayed reactions usually present as serum sickness and infections. Serum sickness tends to occur 5–15 days after onset of thymoglobulin therapy which presents as fever, rash, arthralgia, and/or myalgia, and are treated with corticosteroids. Despite these adverse effects, thymoglobulin has been shown to be safe in renal transplant recipients when administered in a planned and monitored setting.

Thymoglobulin and Infectious Complications

Infectious complications include cytomegalovirus (CMV) infection (13.4%), sepsis (12.2%), candidiasis (3.7%), herpes simplex (4.9%) and urinary infections (18.3%). These infectious episodes were present when the total dose of thymoglobulin was >7 mg/kg [42].

Although most studies have shown a tendency to lower the incidence of CMV infections with basiliximab (Simulect®; Novartis Pharmaceuticals, Surrey, UK) compared to thymoglobulin [43, 44], Brennan et al. [45] in a cohort of 277 patients documented an incidence of CMV at 13.2% in the basiliximab group compared 7.1% in the ATG group. Similarly, a RCT reported a higher incidence of CMV infection in the daclizumab group compared to the thymoglobulin group (18/25 vs. 6/25; $p = 0.03$) [46].

A multicentre, randomised trial using daclizumab (humanised IgG1 monoclonal antibody) versus thymoglobulin showed that the incidence of CMV infection/syndrome/disease was 39 versus 51% in thymoglobulin group ($p = \text{NS}$). Patients and graft survivals and the incidence of biopsy-proven acute rejection (BPAR) were also identical [47].

A prospective, randomised, multicentre study on live donor recipients showed that the overall incidence of infections was comparable between the thymoglobulin group (39.8%) and in no antibody at induction (45.8%, $p = \text{NS}$) [48]. There was no difference in the immunosuppressive regimen between the groups.

Role of Thymoglobulin in Ischemia-Reperfusion Injury

Ischemia-reperfusion injury (IRI) is an acute inflammatory process by which transplanted cells and organs are damaged first by ischemia and later by reperfusion, which leads to cell dysfunction and cell death [49]. The pathogenesis of renal IRI is multifactorial and initially relates to the hypoxic and anoxic cell injuries during the ischemic phase, followed by inflammatory responses during the reperfusion phase. The T cells have been attributed to play a significant role in the pathogenesis of renal IRI [50–52]. Studies have shown both direct and indirect blockade of T cells reduced renal functional and structural injury in murine renal IRI models [51–53]. In athymic nu/nu mice (T-cell knockout mouse strain) subjected to IRI, not only protection from initial renal injury but also an adoptive T-cell transfer into these mice restored the renal injury [54]. Inactivation of these cells is a prerequisite to achieve some protection against IRI [54].

IRI is associated with an increased rate of AR, primary non-function, delayed graft function (DGF) and also late graft failure leading to graft loss [41, 55]. Beiras-Fernandez et al. [56] performed a study in cynomolgus monkeys to evaluate the effect of ATG following IRI. This study demonstrated that the expression of all adhesion mole-

cules (ICAM-1, VCAM, PECAM, CD11b, and CD62e) were significantly lower when compared to the control group. The expression of IL-1, IL-6 and TNF- α were also reduced in ATG group.

Jang et al. [57] investigated the effect of mouse ATG (mATG) in a mouse renal IRI model to assess the effect of mATG following warm renal IRI. Though the mATG effectively depleted the circulating T cells, it seemed to have less effect on kidney-infiltrating T cells. Similarly, there was no difference in serum creatinine, tubular damage and tubular regeneration. mATG did not alter the expression of cytokines (IFN- γ , IL-10). Larger amounts of mATG were needed to achieve a similar degree of T-cell depletion effect as seen in patients treated with smaller doses of ATG, hence limiting a direct implication of these results to a clinical setting.

Role of Thymoglobulin in Prevention of Delayed Graft Function (table 1)

DGF is defined as a need of dialysis in the first week following transplantation. The incidence of DGF depends on multiple factors including obesity, high donor creatinine, panel-reactive antibody (PRA), race, old donor or recipient age, and long cold ischemia time. A randomised, double-blinded study [1] showed that a 7-day induction course with polyclonal rATG resulted in a less frequent and less severe rejection, better event-free survival, and fewer serious adverse events compared with induction with polyclonal eATG (Atgam). In this study, the authors suggested that the intraoperative administration of rATG may have helped to decrease DGF and possibly by blocking the adhesion molecules that play a role in IRI.

However, in another prospective, randomised, international study on high-risk recipients of deceased donors, similar findings could not be replicated [45]. Here patients were randomly assigned to receive either rATG (1.5 mg/kg b.w. daily, 141 patients) during transplantation (day 0) and on days 1 through 4 or basiliximab (20 mg, 137 patients) on days 0 and 4. Although thymoglobulin reduced the incidence and severity of AR, it did not show any effect on the incidence of DGF.

Goggins et al. [58] conducted a randomised, clinical trial of intraoperative versus post-operative thymoglobulin in adult deceased donor renal transplant recipients. This study showed that intraoperative administration before allograft reperfusion is associated with a significant decrease in DGF, a better early allograft function in the first month post-transplant, and a decrease in post-trans-

Table 1. Role of Thymo in DGF

Study (country) period	Time of usage and numbers	DGF	BPAR	Graft survival 1 year	Patient survival 1 year	Comments
Brennan et al. [1] (USA), 1996–1997	At induction and 7 days following transplantation Thymo = 48 Atgam = 24	1% incidence of DGF in total	Thymo = 4% Atgam = 25% ($p = 0.014$) BPAR = Thymo < Atgam (RR = 0.09; $p = 0.009$)	98% 83%	98 ± 2% 96 ± 4%	Double-blind randomised study: high-risk (DD+LD) recipients Rejection was less severe in Thymo than Atgam ($p = 0.014$)
Goggins et al. [58] (USA), 2001–2002	Intra- vs. post-operative Thymo	14.5% 35.5% ($p = 0.05$)	3.6% 16% ($p = 0.11$)	N/A	N/A	DD recipients Prospective randomised study 3–6 doses Thymo was during the 1st week
Patel et al. [59] (USA), 2004–2005	Intra- and post-operative administration with total of 3–7 doses	N/A	N/A	N/A	97% 98%	Retrospective study: DD recipients BPAR at 36 months was 11% non-DGF group and 22.4% in DGF group ($p = 0.025$)
Noël et al. [60] (France and Belgium), 2001–2005	Pre- and post-operative therapy Thymo = 114 Dac = 119	31.5% 44.6% ($p = 0.04$)	15% 27.2% ($p = 0.01$)	17.7% 14%	No difference	Prospective multicentred trial: high immunological DD recipients Tacrolimus, MMF and steroids immunosuppression
Lebranchu et al. [43] (France), 1998–2000	Pre- and post-operative therapy Thymo = 50 Bas = 50	6% 14% ($p = \text{NS}$)	8% 8%	94%	98%	Open, randomized, multicentre study: DD recipients Delayed introduction of CsA, MMF and steroids in the Thymo group
Abou-Ayache et al. [47] (France), 2008	Pre- and post-operative therapy Thymo = 55 Dac = 54	36% 32%	14.5% 16.7%	98% 94%	98% 95%	Prospective, randomized, multicentre trial Delayed introduction of CsA, MMF and steroids in the Thymo group

Thymo = Thymoglobulin; Dac = Daclizumab; Bas = Basiliximab; DGF = delayed graft function; BPAR = biopsy-proven acute rejection; CsA = cyclosporine; DD = deceased donors; LD = live donors.

plant hospital length of stay. The dose-dependent depletion of T cells achieved by rATG [42] may also play a role in the attenuation of graft IRI.

Patel et al. [59] demonstrated that a high BMI (>30), sirolimus-based regimen, female to male donation and donor creatinine >1.5 mg/dl are independent risk factors for DGF. The patients with DGF had a worse survival compared to non-DGF group at 1 year. Patients with moderate PRA (10–50%) to a high (>50%) level of sensitisation who received ATG had fewer incidences of DGF and BPAR, indicating an impact for induction therapy.

A multicentre trial on high-risk deceased donor kidney recipients showed that the incidence of DGF was low in patients who received thymoglobulin compared with daclizumab [60]. The incidence of DGF was 31.5 and 44.6% in the thymoglobulin and daclizumab groups, respectively. More significantly, the incidence of rejection is also low in patients receiving thymoglobulin (15 vs. 27.2%; $p = 0.01$).

Another randomised study investigated the role of thymoglobulin versus basiliximab on deceased donor renal transplant recipients; here the thymoglobulin group had delayed introduction of cyclosporine [43]. The incidence of DGF and BPAR was similar in both groups. Similar findings were reported in another multicentre prospective study by Abou-Ayache et al. [47].

Role of Thymoglobulin on Biopsy-Proven Acute Rejection (table 2)

Two events occurring early in the post-transplantation period, AR and DGF, negatively affect graft survival [61, 62]. Patients with DGF have an increased risk of AR, and graft survival is superior in patients who have neither DGF nor AR [63, 64].

Brennan et al. [45] conducted a prospective, randomised, international, multicentre study to compare short courses of thymoglobulin and basiliximab in high-

Table 2. Role of Thymo in BPAR

Study (country) period	Time of usage and numbers	DGF	BPAR	Graft survival 1 year	Patient survival 1 year	Comments
Brennan DC et al. [45] (USA), 2006	Bas (days 0 & 4) Thymo (days 1 & 4) Thymo = 141 Bas = 137	Thymo = 40.4% Bas = 44.5% (p = NS)	Thymo = 15.6% Bas = 25.5% (p = 0.02)	9.2% 10.2%	95.7% 95.6%	Prospective randomised trial: DD recipients BPAR was less severe in Thymo than Bas (p = 0.02)
Martin et al. [65] (USA), 2004–2007	At induction Thymo = 68 Bas = 31	N/A	Thymo = 7% Bas = 26% (p = 0.02)	0% 3% (p = 0.31)	2% 0%	Single-centre, retrospective study: DD or LD recipients Thymo = ↓ frequency and delayed onset of BPAR
Kamel et al. [66] (Ireland), 1986–1998	63 patients received none Thymo = 59 on 6–10 days	N/A	19.7% 3.3% (p = 0.008)	N/A	62% 90% (p = 0.001)	Retrospective study: DD recipients Thymo ↑ graft survival
Tian et al. [68] (China), 2009	Induction with Thymo versus no inducing agents	N/A	BPAR at 6 months (RR 0.68; 95% CI 0.49–0.96) at 1 year RR 0.70; 95% CI 0.57–0.84)	N/A	N/A	Meta-analysis of randomised controlled trials There was no statistical difference in PS or GS rates at 6 and 12 months
Brennan DC et al. [1] (USA), 1996–1997	At induction and 7 days following Tx Thymo = 48 Atgam = 24	1% incidence of DGF in total	Thymo = 4% Atgam = 25% (p = 0.014) BPAR in Thymo < Atgam (RR = 0.09; p = 0.009)	98% 83%	98 ± 2% 96 ± 4%	Double-blind randomised study: high-risk (DD+LD) recipients. BPAR was less severe in Thymo than Atgam (p = 0.014)
Knight et al. [70] (USA), 1998–2002	Pre- and post-operative therapy Thymo = 30 Bas = 115	14% had DGF	Thymo = 3% Bas = 26% (p = 0.01)	88%	94%	Retrospective study: high-risk DD recipients
Libório et al. [71] (Brazil), 2002–2009	Pre- and post-operative therapy Thymo = 88 Dac/Bas = 79	35.2% 32.9%	11.4% 25.6% (p = NS)	95.5% 83.5% at 5 years	99% 97.2% at 3 years	Retrospective study: DD recipients with an aim to early steroid withdrawal
Cianco et al. [72] (USA), 2002–2004	Pre- and post-operative therapy Thymo = 30 Cam = 30 Dac = 30	13.3% 6.7% 6.7%	16.6% 16.6% 16.6%	92% 100% 88% (p = NS)	88% 100% 88% (p = NS)	Randomised study: DD recipients. Campath arm: 80% steroid-free at 1 year No difference in PS or GS rates at 6 and 12 months

See table 1 for abbreviations.

risk recipients for AR or DGF. The incidence and severity of AR was lower in the thymoglobulin group than in the basiliximab group. The study also showed the incidence of BPAR among patients who received basiliximab was more than 1.5 times than among those who received thymoglobulin. The incidence of CMV disease was lower in the ATG group than in the basiliximab group with appropriate prophylaxis in high-risk patients. Similarly, Martin et al. [65] showed that induction with rATG was associated with a lower frequency and delayed onset of BPAR when compared to a similar cohort of patients receiving.

Kamel et al. [66] reported that ATG increases the transplantation cost initially, but it is eventually offset by a decrease in overall immunosuppressive and rehospitalisation costs. Shenoy et al. [67] have recently published that ATG therapy in corticosteroid-resistant acute allograft rejection is associated with reversal of rejection and excellent graft outcome in paediatric transplants.

A recent meta-analysis of randomised trials has confirmed the role of ATG in prevention of AR episodes and chronic rejection responses after renal transplantation [68]. In addition, a multivariate analysis on antibody induction also confirmed reduction in BPAR [69]. A dou-

Table 3. Role of thymoglobulin in live donor transplantation

Study (country) period	Time of usage and numbers	DGF	BPAR	Graft survival 1 year	Patient survival 1 year	Comments
Hardinger et al. [75] (USA), 1996–2003	Thymo = 214	0%	2% rejection at 1 year	8%	92%	Retrospective study Better outcomes compared with the national statistics
Woodle et al. [48] (USA), 2010	Thymo = 103 No Thymo = 48	1.9% 2.1%	Thymo = 13.9% No Thymo = 19.4% (<i>p</i> = NS)	No difference	No difference	Multicentre, prospective randomised study
Gaber et al. [76] (USA), 2003–2008	Thymo = 2,322	N/A	8.3%	98.2%	98.4%	Multicentre, prospective study on in LD transplantation (Tailor Registry)
Schenker et al. [77] (Germany), 2002–2010	Single-dose Thymo at induction Living related = 60 Living unrelated = 40	N/A	17% 35% (<i>p</i> = 0.035)	93% 95%	97.4% 98.3%	Retrospective case series Incidence of CMV infection (10%), polyomavirus infection (5%), malignancy (4%), and PTLD (0%)
Ciancio et al. [78] (USA), 2002–2006	Pre- and post-operative therapy Thymo = 13 Cam = 13 Dac = 12	N/A	0% 13% 12%	100% (all groups)	100% 93% 100%	Prospective, randomised study Biopsy-proven chronic allograft injury was higher in Campath (23%) vs. Thymo (0%; <i>p</i> = 0.01).

Cam = Campath (1H); LD = live donors; CMV = cytomegalovirus; PTLD = post-transplant lymphoproliferative disorder. See table 1 for further abbreviations.

ble-blinded randomised study on high-risk recipients demonstrated that thymoglobulin was superior in preventing BPAR compared with Atgam (4 vs. 25%; *p* = 0.009) [1]. This finding was also supported by a retrospective study where thymoglobulin versus basiliximab was investigated in high-risk deceased donor recipients [70].

An interesting study investigated the use of thymoglobulin versus daclizumab/basiliximab in a deceased donor kidney recipient where the aim of early withdrawal failed to show any difference in the incidence of BPAR (11.4 vs. 25.6%; *p* = NS) [71]. A similar finding was reported in another randomised study [72]. These studies have demonstrated the feasibility of these agents in an early steroid withdrawal without increasing the risk of rejection.

Thus, most studies have shown thymoglobulin usage to be superior in preventing BPAR when compared with other agents in high-risk patients, without increasing the risk of opportunistic infections and post-transplantation lymphoproliferative disease [45].

Role of rATG in Live Donor Transplantation (table 3)

Live donor renal transplantation was believed to be associated with a lower incidence of BPAR, which is not the case. In 2003, a retrospective Australian study [73] of

498 kidney transplant recipients showed a higher incidence of AR in live donor recipients than in deceased donor renal transplant recipients (44 vs. 28%, respectively, *p* = 0.001). In this study, induction therapy was given only to recipients considered at high risk for rejection (8 vs. 20%). Similar observations were also noted in another study [74].

A retrospective analysis of 214 patients induced with rATG [75] showed that DGF was statistically lower (0% centre cohort vs. 5% national data, *p* = 0.001). The 1-year AR rate was 2% in the centre cohort versus 21% in national data (*p* < 0.001). A recent study conducted using thymoglobulin versus basiliximab monoclonal antibody in live donor renal transplantation has shown that thymoglobulin was associated with a decreased risk of BPAR with no difference on graft survival at 5 years [69].

A prospective, randomised, multicentre study evaluated the early corticosteroid withdrawal (ECSWD) with thymoglobulin in living donor kidney transplantation [48]. In this study the authors reported ECSWD with thymoglobulin induction to chronic corticosteroid therapy (CCST) without antibody induction in primary, living donor renal transplant recipients. Among 151 recipients, 103 received thymoglobulin (ECSWD group) and 48 received no antibody therapy at induction (CCST). There

were no significant differences in BPAR, graft loss, and death at 6 months (85.4 vs. 85.4%) or 12 months (84.4 vs. 74.4%) in the ECSWD group versus the CCST group. No differences were observed in serious adverse events or infectious complications, with the exception of a higher incidence of leukopenia with ECSWD.

A recent prospective, multicentre study that assessed the efficacy of thymoglobulin in live donor transplants reported a low incidence of BPAR (Tailor Registry) [76]. Schenker et al. [77] performed a retrospective study on live donor recipients who had received a single dose of thymoglobulin before transplantation, and demonstrated the beneficial effect thymoglobulin on reducing the BPAR without increasing the incidence of CMV infection. Another comparative study investigated thymoglobulin versus alemtuzumab (Campath-1H) in living donor recipients who showed no difference in the incidence of BPAR, graft survival and patient survival [78].

DGF following live donor renal transplantation is not uncommon and this can be reduced significantly by using thymoglobulin [75]. Usage of thymoglobulin in live donor recipients is not only safe, but it is well established for reducing BPAR.

Role of Thymoglobulin on Graft Survival and Patient Survival Rate

Both DGF and AR in the first year are independent risk factors for graft survival. A retrospective study showed an increased long-term graft survival in patients treated with ATG [79]. In this study the ATG group consisted of high-risk recipients including more hypersensitized, younger patients, second transplant, and cadaveric donors. The final endpoint, a better long-term graft survival was observed ($p = 0.003$). This benefit was independent of recipient age, race and gender, primary cause of renal failure, pretransplant dialysis time, immunological risk, HLA mismatch, donor age, gender and occurrence of DGF. A similar finding has been reported in another study [80]. Shenoy et al. [67] showed that ATG therapy in early-onset corticosteroid-resistant AR is associated with an excellent graft outcome in children. Thus it appears that rATG increases graft survival even in high-risk patients and this result is independent of other risk factors. Hardinger et al. [75] showed that the patient survival rate (live donor transplants) was improved with thymoglobulin (96% centre cohort vs. 90% national data; $p = 0.03$).

Interleukin-2 Receptor Antibody versus Thymoglobulin in Renal Transplantation

Basiliximab is a chimeric monoclonal antibody (murine/human) with human IgG1 constant heavy chain regions and κ light chain. It specifically binds and blocks CD25 antigen, IL-2 α -chain, at the surface of activated T lymphocytes.

A well-structured, prospective, randomised, international study compared a short course of thymoglobulin and basiliximab in patients at high risk of AR or DGF who received a kidney from deceased donors [45]. All patients received cyclosporine, mycophenolate mofetil and prednisolone as maintenance immunosuppression. Thymoglobulin was given 1.5 mg/kg on day 0 and days 1 through 4, and basiliximab 20 mg intravenously on days 1 and 4. The thymoglobulin group had a lower incidence of BPAR (15.6 vs. 25.5%; $p = 0.02$) when compared with the basiliximab group. The severity of the AR was lower in the thymoglobulin group than the basiliximab group. Other than this, graft loss, DGF, CMV disease and death were similar in both groups.

However, since this study was published, tacrolimus has been widely used and has replaced cyclosporine. Willoughby et al. [81] performed a retrospective analysis on 19,137 patients to compare the graft outcomes according to antibody induction regimens within registrar data of the Organ Procurement and Transplantation Network (OPTN). The primary outcome was the 6-month composite endpoint of rejection, graft failure, or death. Thymoglobulin was shown to be associated with a superior outcome compared to basiliximab, but there is to date no RCT available to weigh thymoglobulin versus basiliximab in tacrolimus-based immunosuppression.

A multicentre, randomised study [82] specifically addressed the use of an anti-CD25 monoclonal antibody – daclizumab (Zenapax[®]; Hoffmann-La Roche, Basel, Switzerland) versus thymoglobulin in high-risk renal transplant recipients (TAXI Study). High-risk recipients were defined as PRA >30%, peak PRA >50%, loss of kidney from rejection within last 2 years of transplantation, or two or three previous grafts. Thymoglobulin was administered daily between day 0 and day 7 at a dose of 1.25 mg/kg/day and five injections of daclizumab were administered at a dose of 1 mg/kg on days 0, 14, 28, 42 and 56. The maintenance immunosuppression was tacrolimus, mycophenolate mofetil and steroids and the primary endpoint was BPAR. The thymoglobulin group had a lower incidence of both BPAR (15.0 vs. 27.2%; $p = 0.016$) and steroid-resistant rejection (2.7 vs. 14.9%; $p = 0.002$) at 1 year.

One-year graft and patient survival rates were similar in the two groups. A comparison of rejecters and non-rejecters showed that overall graft survival was significantly higher in the rejection-free group (87.2 vs. 75.0%; $p = 0.037$). The DGF occurred in 31.5% of thymoglobulin group and 44.6% in the daclizumab group ($p = 0.04$). The study concluded that thymoglobulin is superior to daclizumab for the prevention of BPAR among high-immunological-risk renal transplant recipients. No difference in the incidence of CMV infection was seen between these groups. This result was supported by another multicentred RCT which showed no difference in the incidence of CMV infection/syndrome/disease at 1 year, although the mean number of pp65-positive cells was lower in the daclizumab group [47]. However, this trial used a cyclosporine-based maintenance immunosuppression regimen.

Alemtuzumab versus Thymoglobulin in Renal Transplantation

Alemtuzumab (MabCampath or Campath; Genzyme) is humanised rat monoclonal CD52 antibody that causes prolonged and sustained lymphopenia [83]. It specifically acts on mononuclear cells [84] and has been used as a therapeutic agent in solid organ transplantation but is limited to B-cell chronic lymphocytic leukaemia [85, 86]. Thomas et al. [87] addressed its use in a prospective RCT on recipients with high immunological risks. Recipients received either a single dose of alemtuzumab before the graft perfusion with tacrolimus monotherapy or four doses of thymoglobulin. One-year cumulative graft survival was 85.7% for the alemtuzumab group and 87.5% for the thymoglobulin group. The infection and rejection rates were not different between these groups.

Another interesting randomised trial [72] was done using three different antibodies at induction and primarily to assess the safety of alemtuzumab with a lower dose of tacrolimus, mycophenolate mofetil and steroid avoidance. Groups A, B and C received thymoglobulin, alemtuzumab and daclizumab, respectively. Maintenance immunosuppression included tacrolimus and mycophenolate in all three arms and steroids in groups A and C only. There was no difference in BPAR, CMV infection rate, patient and graft survival.

A recent prospective study evaluated the efficacy of alemtuzumab in high- and low-risk patients compared to basiliximab and thymoglobulin [88]. Among 139 high-risk patients, 70 received alemtuzumab (one dose of 30 mg) and 69 had thymoglobulin (a total of 6 mg/kg b.w.

given over 4 days). The 335 low-risk patients received alemtuzumab (one dose of 30 mg in 164 patients) or basiliximab (a total of 40 mg over 4 days in 171 patients). All patients received tacrolimus and mycophenolate mofetil and underwent a 5-day steroid taper in a regimen of early steroid withdrawal. The rate of BPAR was significantly lower in the alemtuzumab group than in the conventional therapy group at both 6 months (3 vs. 15%, $p < 0.001$) and 12 months (5 vs. 17%, $p < 0.001$). At 3 years, the rate of biopsy-confirmed AR in low-risk patients was lower with alemtuzumab than with basiliximab (10 vs. 22%, $p = 0.003$), but among high-risk patients, no significant difference was seen between alemtuzumab and thymoglobulin (18 vs. 15%, $p = 0.63$). Adverse event rates were similar among all four treatment groups. Kaplan-Meier actuarial estimated patient survival among the study patients was 96% with alemtuzumab and 96% with conventional therapy ($p = 0.38$). Among the high-risk patients, graft survival was 91% with alemtuzumab and 84% with rATG ($p = 0.32$). After censoring of data on deaths, the estimated rates of graft survival among high-risk patients were 91% with alemtuzumab and 91% with rATG ($p = 0.88$).

The above findings were confirmed by a recent systematic review and meta-analysis [83] from ten randomised clinical trials that showed alemtuzumab induction has a lower risk of positive BPAR compared with induction with basiliximab and daclizumab combined [relative risk 0.54; 95% confidence interval (CI) 0.37–0.79; $p < 0.01$]. However, no significant difference was observed in the risk of BPAR when alemtuzumab induction was compared with thymoglobulin ATG-Fresenius S (Fresenius, Munich, Germany) (relative risk 0.79; 95% CI 0.52–1.21; $p = 0.28$). There was no difference in graft loss, DGF, patient death, and new-onset diabetes mellitus after transplantation when alemtuzumab was compared with IL-2 receptor antibodies or thymoglobulin induction.

Alemtuzumab induction thus reduces the risk of BPAR when compared with IL-2 receptor antibodies but not thymoglobulin, and the benefits of both have not yet been studied to address their role in donation after circulatory death (DCD) transplantation.

Thymoglobulin versus Eculizumab (Inhibitor of Terminal Complement Activation) in Renal Transplantation

The data of Goh et al. [89] from Mayo Clinic combined eculizumab and rATG for patients with a baseline T- and/or B-cell FXM channel shift >300 who underwent pre-

transplant plasma exchange (PE) treatments to achieve both T- and B-cell FXM channel shifts >300 on the day of transplant. They compared it with a group receiving anti-IL-2 antibody having no pre-transplant donor-specific antibody and rATG alone for kidney transplant recipients who were high risk but had both negative T- and B-cell flow cytometric cross-matches (FXM). They reported that, compared to the anti-IL-2 receptor antibody induction group, both groups treated with rATG demonstrated significant depletion of all T-cell subsets (CD3-positive cells) ($p = 0.0001$ for rATG vs. the anti-IL-2 receptor antibody induction group; $p = 0.001$ for rATG + eculizumab vs. the anti-IL-2 receptor antibody group). However, while T-cell counts were low in all rATG-treated patients, eculizumab treatment resulted in higher peripheral blood T-cell counts in rATG-treated patients ($p = 0.005$). They concluded that eculizumab appears to have a mild inhibitory effect on peripheral blood T-cell depletion by rATG in kidney transplant recipients. The combination of rATG + eculizumab has added use in positive cross-match kidney transplants without increasing the risk of ACR compared to the control group similar to other studies ($p = 0.0031$) [90]. These observations are consistent with the findings of previous in vitro studies that in vivo T-cell depletion by rATG in kidney transplant recipients might be partly but not entirely dependent on the complement.

Does Thymoglobulin Increase Risk of Post-Transplant Lymphoproliferative Disorder?

Post-transplant lymphoproliferative disorder (PTLD) is a relatively rare but well-known complication after organ transplantation. The recognised risk factors for PTLD are Epstein-Barr virus (EBV) serology and use of a potent immunosuppressive regimen [91–95]. Exposure to a newer and potent immunosuppression has led to a trend towards increasing the incidence of PTLD and earlier occurrence of PTLD [91, 92, 96]. Opelz et al. [97] showed that patients receiving thymoglobulin had a significant increased risk of lymphoma probably caused by inhibition of T-cell control which allows the uninhibited growth of B cells. Other studies however claim that thymoglobulin use in lower doses does not increase the risk of PTLD [58, 75, 98].

Unfortunately, up-to-date literature only highlights a few studies to assess this problem. Dharnidharka and Stevens [99] analysed the UNOS (United Network for Organ Sharing) data of 87,407 patients and showed that male

gender and Caucasian were associated with a significantly high relative risk for PTLD. In an adjusted analysis, the adjusted relative risk for PTLD development was significantly higher with the eATG or ALG but not with rATG. There was however no EBV serology data available from UNOS for further analysis.

Caillard et al. [91] who retrospectively analysed 25,127 patients reported that recipient age <20 years, pre-transplant malignancy, higher HLA match, and occurrence of rejection in the first year were associated with the development of PTLD. In addition, OKT3 usage was associated with a greater risk of PTLD, but not thymoglobulin. The authors do highlight a possible limitation in that the number of patients who received thymoglobulin was small ($n = 684$). Further subanalysis showed a quadruple immunosuppressive regimen and patients who received tacrolimus versus cyclosporine are at increased risk of developing PTLD, suggesting that the culprit is probably a high immunosuppressive burden.

Another recent study in a cohort of 53,719 patients had shown that Caucasian, EBV-negative recipients, de novo sirolimus treatment, recipient with history of malignancy and rejection within the first year of transplantation were associated with a high risk of PTLD. The African-American kidney transplant recipients were at lower risk of developing PTLD irrespective of recipient EBV status [100]. Although the use of monoclonal and polyclonal agents per se did not increase the risk of PTLD, when used with calcineurin inhibitors the risk increased significantly.

A recent prospective, randomised, double-blinded study by Hardinger et al. [101] showed that there is no increase in the incidence of cancer and PTLD. Overall, there was a lower incidence of non-cutaneous malignancy in the thymoglobulin group compared to the Atgam group at 10 years of follow-up (6 vs. 17%, $p = \text{NS}$). There were no cases of PTLD in the thymoglobulin group and 2 cases in the Atgam group. This is the only study with a 10-year follow-up after thymoglobulin induction. Brennan et al. [45] observed similar findings, there being no significant difference in the incidence of cancer (including PTLD) when comparing with basiliximab. However, Kirk et al. [102] have shown that the overall incidence of PTLD was 0.42% and differed significantly by induction strategy ($p = 0.01$) (without induction (0.43%), basiliximab (0.38%), daclizumab (0.33%), thymoglobulin (0.67%), and alemtuzumab (0.37%)). Thymoglobulin was associated with a significantly increased PTLD risk ($p = 0.0025$), but alemtuzumab ($p = 0.74$) and basiliximab ($p = 0.33$), which trended toward a protective effect ($p = 0.06$), were not. It has also been noted in these studies that

PTLD is more clearly related with a maintenance immunosuppressive regimen rather than use of any particular drug. Reduction of this immunosuppression burden is thus associated with a decrease in the risk of PTLD [45, 102].

Dosing of Thymoglobulin

The initial trials establishing efficacy and safety of rATG were conducted using doses starting at 10.5 mg/kg [1, 103]. Full-dose rATG induction therapy (7–10 mg/kg) has been associated with increased morbidity in the early post-transplant period [42, 104]. An attempt at establishing a lower dosing regimen for rATG has been described in several studies [105–107].

Hardinger et al. [106] reported the results of induction with rATG 3 mg/kg intra-operatively followed by 1.5 mg/kg on POD 1 and 2 in 40 renal transplant recipients as compared with a historical control group. Patients were generally low-risk and this study did show the efficacy of induction therapy (low dose) with a short course of rATG. In an attempt to establish an optimal dose, Wong et al. [108] evaluated the degree and durability of T-cell clearances with two different thymoglobulin regimens in adult kidney transplant recipients: group I had a 3-day thymoglobulin-based induction of 1.0 mg/kg/day, while group II received 1.5 mg/kg/day in addition to maintenance immunosuppression. They concluded that thymoglobulin induction was efficacious in both groups, but with a significantly sustained T-cell clearance in the 1.5-mg/kg/day regimen up to the first 6 months post-induction therapy. They suggested that this may translate into a decreased risk of immunological injury and possibly improve the long-term outcome after kidney transplantation.

Interestingly, Büchler et al. [109] in an attempt to optimise the dose and regimen of rATG, administered rATG at a total dose of 6 mg/kg, administered either as 1.5 mg/kg/day on days 0–3 (group 1) or 3 mg/kg on days 0 and 3 (group 2). They showed that rATG induced a significant decrease in the proportion of naive CD4⁺ T cells, which plateaued after month 1 in group 1 and after month 6 in group 2 and concluded that their results suggest that the dosing regimen for rATG induction influences pharmacokinetic parameters without affecting the quality of immune reconstitution.

Low-Risk Recipients

Laftavi et al. [110] explored the benefit and risks associated with low-dose rATG (rATG; 3–5 mg/kg total vs.

basiliximab) induction in a low-risk population. They showed that in recipients of live donor kidneys, 8-year patient and graft survivals were not different; however, low-dose rATG was associated with a lower rate of AR (7.8 vs. 35% basiliximab, $p < 0.01$) and better mean serum creatinine at 3 and 5 years (1.2 vs. 1.5, $p = 0.02$ and 1.18 vs. 1.54, $p = 0.04$, respectively). For deceased donor recipients, low-dose rATG was associated with a better long-term graft survival (86 vs. 76% basiliximab, $p = 0.02$). Djamali et al. [111] showed that two immunosuppressive regimens based on rATG given daily or intermittently following the CD3⁺ T lymphocytes (measured by flow cytometry) offered similar T-cell depletion and effective immunosuppression, thus supporting low-dose intermittent ATG induction as there was no significant difference in renal graft function, the number of acute graft rejections, or ATG-related side effects and complications and a net saving of USD 760 per patient.

High-Risk Recipients

Klem et al. [112] have used rATG at 1.5 mg/kg/day for 3 doses (group I) or 4 doses (group II) to determine the impact of reduced exposure rATG in the prevention of AR. They reported 1-year AR rates were 10 and 11% in the 3- and 4-dose cohorts, respectively, with 100% patient and graft survival at 1 year in both groups. They concluded that excellent protection against AR, even in patients at increased risk, can be achieved with the potential for cost savings from a reduction in hospital stay ($p = 0.004$) and medication administration. Similarly, Gurk-Turner et al. [103] in their regimen assessed group 1 receiving ≤ 7.5 mg/kg rATG and group 2 receiving > 7.5 mg/kg rATG. They showed that the incidence of biopsy-proven AR during the first 12 months did not differ between the groups (9.5 vs. 8.8%, respectively, $p = 0.9$). Serum creatinine at 12 months was 1.6 ± 0.7 in group 1 and 1.8 ± 1.0 in group 2 ($p = 0.3$). There was no independent association between rATG dose and graft survival (hazard ratio 0.85, $p = 0.79$, 95% CI 0.26–2.7 for group 2 vs. group 1) or 1-year SCr (regression coefficient 0.02 for $\ln(\text{SCr})$, $p = 0.3$; 95% CI -0.01 to 0.6), thus concluding that in high-risk kidney transplant recipients, total rATG doses ≤ 7.5 mg/kg are safe and effective in achieving a low rate of AR and graft outcomes comparable to higher doses.

The review of Deeks and Keating [113] highlighted that rATG induction in combination with immunosuppressive therapy is more effective in preventing episodes of acute renal graft rejection in adult renal transplant recipients than immunosuppressive therapy without induction. The efficacy of rATG induction is generally bet-

ter than that of eATG induction and generally no different from that of basiliximab or low-dose daclizumab induction in this patient population. However, in high-risk patients, rATG induction was more effective than daclizumab or basiliximab induction in preventing acute renal graft rejection. Induction with rATG has thus developed with time where initial dosing has been reduced to a low-dose regimen, followed by evidence to suggest a low-dose regimen in the high-risk strategy group.

Other Benefits

The use of thymoglobulin may help to support a calcineurin inhibitor-sparing regimen. Larson et al. [114] conducted a prospective, randomised trial which has shown significant chronic vascular changes on biopsies when a combination of thymoglobulin and calcineurin inhibitors are used. Similarly, thymoglobulin use can help in achieving a steroid-free immunosuppression regimen in renal transplantation without decreasing graft and patient survival [48].

Conclusion

DGF and BPAR at 1 year are independent risk factors for decreased graft survival. The role of thymoglobulin is justified when risk stratification is carried out as it may reduce DGF, AR, could prolong graft survival and patient survival. Studies to assess thymoglobulin induction in patients with a low risk are controversial but a long-term follow-up to assess the impact on BPAR, DGF, patient and graft survival, at risk of PTLT and risk of opportunistic infections justifies a randomised multicentre international long-term follow-up study.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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