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The primary aim of *World Journal of Transplantation* (*WJT*, *World J Transplant*) is to provide scholars and readers from various fields of transplantation with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJT mainly publishes articles reporting research results obtained in the field of transplantation and covering a wide range of topics including bone transplantation, brain tissue transplantation, corneal transplantation, descemet stripping endothelial keratoplasty, fetal tissue transplantation, heart transplantation, kidney transplantation, liver transplantation, lung transplantation, pancreas transplantation, skin transplantation, *etc.*

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MINIREVIEWS

Anti-thymocyte globulin for treatment of T-cell-mediated allograft rejection

Sumit Acharya, Suraj Lama, Durga Anil Kanigicherla

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Abstract

Anti-thymocyte globulin (ATG) is a pivotal immunosuppressive therapy utilized in the management of T-cell-mediated rejection and steroid-resistant rejection among renal transplant recipients. Commercially available as Thymoglobulin (rabbit-derived, Sanofi, United States), ATG-Fresenius S (rabbit-derived), and ATGAM (equine-derived, Pfizer, United States), these formulations share a common mechanism of action centered on their interaction with cell surface markers of immune cells, imparting immunosuppressive effects. Although the prevailing mechanism predominantly involves T-cell depletion *via* the complement-mediated pathway, alternate mechanisms have been elucidated. Optimal dosing and treatment duration of ATG have exhibited variance across randomised trials and clinical reports, rendering the establishment of standardized guidelines a challenge. The spectrum of risks associated with ATG administration spans from transient adverse effects such as fever, chills, and skin rash in the acute phase to long-term concerns related to immunosuppression, including susceptibility to infections and malignancies. This comprehensive review aims to provide a thorough exploration of the current understanding of ATG, encompassing its mechanism of action, clinical utility in the treatment of acute renal graft rejections, specifically steroid-resistant cases, efficacy in rejection episode reversal, and a synthesis of findings from different eras of maintenance immunosuppression. Additionally, it delves into the adverse effects associated with ATG therapy and its impact on long-term graft function. Furthermore, the review underscores the existing gaps in evidence, particularly in the context of the Banff classification of rejections, and highlights the challenges faced by clinicians when navigating the available literature to strike the optimal balance between the risks and benefits of ATG utilization in renal transplantation.

Key Words: Anti-thymocyte globulin; T-cell-mediated rejection; Steroid-resistant

rejection; Biopsy confirmed acute rejection

Core Tip: Anti-thymocyte globulin is a highly efficient induction agent that can prevent acute rejection and delayed graft function. It is widely used for biopsy confirmed acute rejection reversal and steroid-resistant rejection.

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INTRODUCTION

Rejection is one of the common complications after kidney transplantation. About 10%-20% of kidney transplant recipients experience acute rejection (AR) in the first year post-transplant[1,2]. AR can be defined clinically as a rise in serum creatinine in the absence of other pathology, and verified by allograft biopsy using the Banff classification system [3]. AR is associated with an increased risk of long-term graft loss, morbidity, and mortality[4]. Therefore, timely treatment of AR is crucial in improving long-term outcomes in kidney transplantation. A proportion of AR can be resistant to steroids (25%-30% of AR episodes)[2]. Anti-thymocyte globulin (ATG) is a polyclonal antibody used as an induction agent to reduce rejection rates and treat rejections following a kidney transplant. It is available in rabbit-derived (rATG; Thymoglobulin), ATG-Fresenius, and equine-derived forms (eATG; ATGAM). During the early use of ATG, its role in treating steroid-resistant allograft rejection was established[5]. The Kidney Disease Improving Global Outcomes (KDIGO) and British Transplant Society guidelines advise using ATG at induction in high-risk individuals and as an option to manage steroid-resistant acute rejection[6,7]. For this review, we studied peer-reviewed research articles published in PubMed-indexed journals. We reviewed the various clinical trials of ATG, its use in the treatment of acute rejection, steroid-resistant rejection, recurrent rejections, and clinical studies published in similar journals. We excluded reports presented as conference abstracts and those published in languages other than English. We aimed to evaluate the risks and benefits of ATG treatment in rejections and its implications in clinical practice. We envisage that such analysis of the literature will help clinicians and patients evaluate the role of ATG holistically in current transplantation protocols and aid in clinical decision-making at an individual patient level. Lastly, we identify gaps in evidence and outline potential strategies that could help bridge these gaps to improve post-transplant patient and allograft survival.

MECHANISM OF ACTION

ATG predominantly targets T cell antigens (although some of these antigens are present in other cell types) like TCR/CD3, CD2, CD4, CD5, CD6, CD8, CD25, CD28, CD45, and HLA (Human Leukocyte Antigen) class I to induce the immunosuppressive effects. The complement-dependent T cell lysis in the intravascular compartment (*i.e.*, blood) and the phagocytosis of T cells by macrophages in peripheral and secondary lymph nodes are regarded as the primary mechanism of action of ATG. The pre-activated T cells present in blood or peripheral tissues are depleted through antibody-dependent cell-mediated cytotoxicity and Fas-ligand-dependent apoptosis pathways[5,8,9]. The pharmacokinetics of ATG depends on the dose and schedule of administration as well as the number of 'targeted' immune effectors[9]. A lower concentration of thymoglobulin in the 0.1–1 μg/mL range induces lysis of preactivated T cells. A higher concentration (10–100 μg/mL) triggers CD178 (CD95-L) expression by resting T cells and apoptosis of preactivated T cells through pathways mostly involving Fas/Fas-L interactions[10,11]. ATG also modulates cell surface expression of adhesion molecules (ICAM-1, -2, and -3), integrins (LPAM-1 and VLA-4), and chemokine receptors (CXCR4, CCR5, and CCR7), thus interfering with leukocyte-endothelial interactions that play a role in ischemia/reperfusion injury, graft *vs* host disease, and rejection[10,12]. The modulation, particularly in this setting, is the process of internalization of the ATG-antigen complex by endothelial cells. This results in decreased surface antigen which ultimately decreases the interaction of leucocytes with the endothelium and their trans-migration into tissue. ATG has been shown to contain antibodies against a few B-cell antigens, including B-cell-specific and non-specific surface proteins CD19, CD20, CD40, CD80, CD30, CD38, CD95, and HLA-DR. ATG crosslinks with these surface proteins and induces apoptosis (*in vitro*) in naïve and activated B cells at clinically relevant concentrations (1–100 ng/mL). ATG can also bind with Syndecan-1 (CD138), a plasma-cell-specific molecule; however, *in vivo* ATG treatment is not associated with a reduction in either splenic or bone marrow plasma cells[5,9].

ATG interferes with the functional properties of dendritic cells (DCs) including maturation and migration and influences the balance between solid organ rejection and tolerance. Several *in vitro* studies showed the tolerogenic effect of ATG. ATG attaches to Toll-like receptors present on the surface of DCs. The common mechanism is the induction of

complement-mediated DC lysis hampering lymphocyte proliferation[13-15].

Finally, ATG is also known to produce dominant tolerance by the expansion of CD4+CD25high Foxp3+ T-regulatory cells which inhibits the action of CD4+CD25- T cells, CD8+ T cells, B cells, DCs, and natural killer (NK) cells[16-18]. It also associates with the increase of NK-T cells (CD4-/CD8- subset of T cells), which seems to decrease the incidence and severity of acute rejection[19]. Figure 1 summarizes the five documented mechanisms of ATG.

TREATMENT OF T-CELL-MEDIATED REJECTION

T-cell-mediated rejection (TCMR) is a process initiated by the interaction of T-cells with donor antigens predominantly presented by macrophages. The interaction of these biomolecules leads to local inflammation (infiltration of T cells and macrophages) that further leads to recruitment of effector T cells, tubulitis, nephron response to injury including differentiation of the epithelium, and if untreated, nephron loss that will be irreversible. Acute rejection is clinically suspected in patients experiencing an increase in serum creatinine, after the exclusion of other causes of graft dysfunction. Subclinical acute rejection is defined by the presence of histological changes specific for acute rejection on screening or protocol biopsy, in the absence of clinical symptoms or signs. Kidney biopsy remains the gold standard test to diagnose acute rejection, with characteristic infiltration of donor tissue interstitium with host T cells, cells in the monocyte-macrophage lineage, and nephron injury[20]. Treatment of TCMR has changed little over time and sparse data exist comparing one strategy to another.

AR requires a short course of more intensive immunosuppression in addition to baseline immunosuppression therapy. Options include treatments with steroids, antibody preparations, alteration of maintenance immunosuppression, or a combination of these options. Corticosteroid therapy is the most commonly used first-line treatment for acute cellular rejection episodes. Although most patients respond to corticosteroids, the dose and duration of treatment have not been well defined by randomised controlled trials. Table 1 lists the published clinical trials and Table 2 lists published cohort studies, the majority of which are retrospective single centre studies. Treatment of acute cellular rejection with T-cell depleting antibody can be more effective in improving kidney function and preventing graft loss than treatment with corticosteroids alone[21]. However, all these trials were published more than 20 years ago, with the majority between 1970s and 1990s, when Banff classification was yet to be incorporated into clinical practice or clinical trials/studies. In clinical practice, treatment is guided by biopsy features as longer-term graft survival varies with the type of TCMR[22]. The majority of Banff class I lesions respond to methylprednisolone alone; conventionally pulse methylprednisolone at 250–500 mg daily for 3–5 d is recommended by international guidelines[6]. TCMR involving lymphocytic infiltrate of the vasculature (Banff II and III lesions) may necessitate T cell–depleting therapy. Polyclonal antibodies include horse-derived (anti-lymphocyte globulin, ALG) and rabbit-derived (ATG) antibodies against the human lymphocyte or thymocyte, respectively. Most commonly rATG dosed at 1.5 mg/kg for 7-14 doses was used (Tables 1 and 2)[8,21-24]. Reversal of rejections was seen in 50%-90% in clinical trials. Intravenous immunoglobulin (IVIG) and anti-thymocyte serum were also used in the past[25]. Recently, Alemtuzumab had been put forward as a possible treatment option for rejection[26].

STEROID-RESISTANT REJECTIONS

In approximately 25% to 30% of the patients, rejections are not reversed with steroid therapy alone. In these recipients, more intensive immunosuppressive therapy is required to reverse the AR episode. When serum creatinine levels do not recover to within 120% of the pre-rejection baseline value following corticosteroid pulse therapy within 14 d of the steroid medication's initiation, the episode is deemed steroid-resistant[27]. Up until day 5, patients with steroid-responsive and steroid-resistant AR experienced similar changes in their serum creatinine levels. However, at that point, the responders' creatinine levels significantly decreased, while the non-responders' levels stayed high. Therefore, conventionally, physicians typically wait 5 d for classifying a rejection as steroid-resistant[28].

ADVERSE EFFECTS

Infusion of ATG may be complicated by immediate toxicity in the form of fever, chills, or skin rash which are considered self-limiting and managed by symptomatic therapy (paracetamol, antihistamines, and bolus steroids) and reducing rates of infusion. Lymphopenia, neutropenia, and thrombocytopenia can occur, but these are amenable to dosage adjustment. Medium- to longer-term effects include cytopenia, higher rates of infection, and malignancy. Serum sickness is a rare complication caused by the deposition of immune complexes in tissues. Characteristic symptoms include fever, jaw pain, arthralgia, lymphadenopathy, and rash[10,22]. Registry studies have tried to determine whether ATG induction therapy is associated with a greater risk of developing post-transplant lymphoproliferative disease, but results are mixed and remain inconclusive[10]. Tables 1 and 2 outline the frequency of these adverse effects published in the randomised controlled studies and cohort studies, respectively.

Table 1 Summary of randomized clinical trial studies

No.	Ref.	Study design	ATG – dose & duration	Graft outcome	Death	Other adverse events
1	Shield *et al* [50], 1979	Prospective, randomised, single centre, United States; First rejection	eATG 15 mg/kg daily for 14 d (n = 10) *vs* MP 1 g/d for 5 d (n = 10)	Reversal – 8/10 (ATG) *vs* 6/10 (MP); Recurrent rejection 1/10 (ATG) *vs* 5/10 (MP); Graft loss at 12 mo – 1/10 (ATG) *vs* 1/10 (MP)	At 12 mo – 0/10 (ATG) *vs* 1/10 (MP)	Infection – 3/10 (ATG) *vs* 0/10 (MP); AVN – 1/10 (ATG) *vs* 0/10 (MP)
2	Filo *et al*[51], 1980	Prospective, randomised, single centre, United States; First rejection	eATG 10 mg/kg/d for 15 d (n = 35) *vs* MP 30 mg/kg every other day up to 5 doses (n = 43)	Reversal – 32/35 (ATG) *vs* 29/43 (MP); Recurrent rejection – 16/35 (ATG) *vs* 15/43 (MP); Graft survival (91% *vs* 62%); Faster recovery (6.9 d *vs* 8.9 d); Graft loss – 15/35 *vs* 25/43 (MP)	At 12 mo – 1/24 (ATG) *vs* 0/29 (MP)	
3	Hoitsma *et al* [52], 1982	Prospective, randomised, single centre, Netherlands; First rejection	rATG initially 4 mg/kg followed by 2-7 mg/kg for 21 d (n = 20) *vs* prednisolone 200 mg/d, tapered to 25 mg/d in 2 wk (n = 20)	Reversal – 43/50 (ATG) *vs* 35/50 (Prednisolone); Recurrent rejection – 28/50 (ATG) *vs* 35/50 (Prednisolone); Graft loss – 15/50 (ATG) *vs* 28/50 (Prednisolone)	At 12 mo – 0/20 (ATG) *vs* 1/20 (Prednisolone)	Infection – 9/20 (ATG) *vs* 15/20 (Prednisolone)
4	Toledo-Pereyra *et al* [53], 1985	Prospective, randomised, single centre, United States; First rejection	ALG 10 to 20 mg/kg for 10 d (n = 20) *vs* ATG 10 to 20 mg/kg for 10 d (n = 20)	Reversal – 15/20 (ALG) *vs* 16/20 (ATG)		
6	Alamartine *et al*[54], 1994	Prospective randomised, single centre, France; Steroid-resistant rejection	Muromonab-CD3 5 mg/d for 10 d (n = 27) *vs* rATG: 1.5 mg/kg/d for 10 d (n = 32)	Reversal – 25/26 (Muromonab-CD3) *vs* 27/32 (ATG); Recurrent rejection – 25/32 (ATG) *vs* 24/27 (Muromonab-CD3); Graft loss at 12 mo – 11/32 (ATG) *vs* 4/26 (Muromonab-CD3)		CMV infection – 8/27 (Muromonab-CD3) *vs* 18/32 (ATG)
7	Tesi *et al*[55], 1997	Prospective, randomised, multi-centre n = 163 (82 Thymoglobulin, 81 ATGAM); First rejection	rATG 1.5 mg/kg *vs* ATGAM 15 mg/kg (both for 7 to 14 d)	65% treated with THYMO had histology grade improvement (*vs* 50% in ATGAM)	Overall – 3/82 (rATG) *vs* 1/81 (eATG)	CMV infection 20/82 in both groups
8	Mariat *et al* [31], 1998	Prospective, randomised, single centre, France; First rejection	Muromonab-CD3 5 mg/kg for 3 d followed by 2.5 mg/kg for 7 d (n = 29) *vs* rATG 25 mg/d if < 40 kg, 50 mg/d if 40-70 kg & 75 mg/d if > 70 kg; 10 d (n = 31)	Reversal – 25/29 (Muromonab-CD3) *vs* 30/31 (ATG); Recurrent rejection – 11/29 (Muromonab-CD3) *vs* 9/31 (ATG); Graft loss at 12 mo – 6/29 (Muromonab-CD3) *vs* 4/31 (ATG)	At 12 mo – 3/31 (ATG) *vs* 1/29 (Muromonab-CD3)	CMV infection – 12/31 (ATG) *vs* 13/29 (Muromonab-CD3); Malignancy – 0/31 (ATG) *vs* 2/29 (Muromonab-CD3)
9	Gaber *et al* [56], 1998	Prospective, randomised, multi centre, United States; First rejection	Thymoglobulin (rATG) 1.5 mg/kg/d for 7-14 d (n = 82) *vs* ATGam (eATG) 15 mg/kg/d, for 7-14 d (n = 81)	Reversal – 88% (Thymoglobulin) *vs* 76% (ATGAM); Recurrent rejection; 28/82 (rATG) *vs* 50/81 (eATG)	Total 6/82 (rATG) *vs* 3/81 (eATG)	Leukopenia – 57% (rATG) *vs* 30% (eATG); Bacterial infection – 29% (rATG) *vs* 37% e(ATG); Viral infection – 21% (rATG) *vs* 11% (eATG)
10	Theodorakis *et al*[57], 1998	Prospective, randomised, single centre, Germany; First rejection	ATG 4 mg/kg for 7 d (n = 25) *vs* MP 250 mg/d for 3 d (n = 25)	Recurrent rejection – 4/25 (ATG) *vs* 18/25 (MP); Graft loss – 5/25 (ATG) *vs* 3/25 (MP)		
11	Baldi *et al* [58], 2000	Prospective, randomised, single center, Belgium; First rejection	rATG 4 mg/kg day for 10 d (n = 28) *vs* Muromonab-CD3: 5 mg/d for 10 d (n = 28); MP for both groups: 500 mg/d for 3 d	Reversal – 21/28 (rATG) *vs* 14/28 (Muromonab-CD3); Recurrent rejection – 9/28 (ATG) *vs* 10/25 (Muromonab-CD3)	Irreversible rejection in 3/28 OKT3, 2nd rejection in 33% ATG, 39% OKT3	Fever – 21.4% (ATG) *vs* 92.8% (Muromonab-CD3); Headache – 3.5% (ATG) *vs* 46.4% (Muromonab-CD3); Infection – 9/28 (ATG) *vs* 10/28 (Muromonab-CD3); Malignancy 2/28 (ATG) *vs* 0/28 (Muromonab-CD3)
12	Midtvedt *et al*[59], 2003	Prospective, randomised, single centre, Norway; First rejection	ATG 2 mg/kg followed by 1 mg/kg if & when T cells > 50 (n = 27) *vs* muromonab-CD3: 5 mg, then 2.5 mg (n = 28)	Reversal – 26/27 (ATG) *vs* 27/28 (Muromonab-CD3); Recurrent rejection – 12/27 (ATG) *vs* 14/28 (Muromonab-CD3); Grafts loss at 12 mo – 3/27 (ATG)	At 12 mo – 2/27 (ATG) *vs* 1/28 (Muromonab-CD3)	CMV infection – 14/27 (ATG) *vs* 11/28 (Muromonab-CD3); Malignancy – 1/27 (ATG) *vs* 1/28 (muromonab-CD3); Bacterial pneumonia – 3/27

			vs 4/28 (Muromonab-CD3)			(ATG) *vs* 3/28 (Muromonab-CD3)

ATG: Anti-thymocyte globulin; rATG: Rabbit Anti-thymocyte globulin, eATG: Equine Anti-thymocyte globulin; MP: Methylprednisone.

Table 2 Summary of non-randomized clinical studies

No	Ref.	Study design	ATG -dose/duration	Graft outcome	Death	Adverse events
1	Hardy *et al* [60], 1980	Prospective, non-randomised, single centre , United States, *n* = 20 (10 ATG)	eATG – 15 mg/kg (max 750 mg) for 21 d + MP (750, 200 & 150 mg for 3 d) (*n* = 10) *vs* MP (750, 200 & 150 mg for 3 d) (*n* = 10)	Reversal – 9/10 (ATG) vs 8/10 (control); Recurrent rejection 2/10 (ATG) *vs* 4/10 (control); Graft loss at 12 mo – 4/10 (ATG) *vs* 5/10 (control)	0 in both groups	3 serious complications in control group and 1 in ATG
2	Richardson *et al*[30], 1989	Prospective, non-randomised, single centre, United Kingdom	rATG (2-3 mg/kg for 5-10 d) reduced to 1-2 mg/kg if leukopenia or thrombocyt-openia (*n* = 27)	70.3% graft survival with mean follow-up time of 13.3 mo; 8 out of 27 failed (6 due to rejection, 1 death, and 1 renal artery stenosis)	1 death	6 UTIs, 1 pseudomembranous colitis, 8 CMV and 5 HSV, 2 deaths
3	Clark *et al* [45], 1993	Prospective, non-randomised, single centre, United Kingdom	Group 1: rATG, 2.5-5 mg/kg/d) for 10-14 d (*n* = 10); Group 2: As per T cell count for 10-14 d (*n* = 17)	76% graft survival at 1 year group 2 (*vs* 60% in group 1); Group 1 – (4 rejections); Group 2 – (4 rejections)	2 deaths (group 1) *vs* 0 deaths (group 2)	Group 1: 3 serious viral infection, 6 minor infections; Group 2: 11 minor infections
4	Uslu *et al* [61], 1997	Retrospective, non-randomised, single centre, Turkey	rATG 5 mg/kg for 13.7 ± 3.7 d (*n* = 9) OKT3 5 mg/d for 11.4 ± 1.9 d (*n* = 5)	Graft survival: 78% ATG *vs* 20% OKT3 with median f/u 405 d		OKT3 – 1 CMV, Fever > 38 in 80% pts in both groups, Leukopenia (35% ATG *vs* 0 in OKT3)
5	Sharma *et al* [46], 2003	Prospective, non-randomized, single centre, India	ATG 1.5-1.8 mg/kg alternate d, mean duration 5 doses (*n* = 33)	90% graft survival in first year and 73% at 20 mo. Graft loss in 4; Recurrent rejection in 8/33 at 3 mo	1 death	11 pneumonia, 3 UTI, 1 peritonitis, 2 CMV, 5 leukopenia
6	Colak *et al* [62], 2008	Retrospective, non-randomised, single-centre, Turkey	ATG 3-5 mg/kg/d 10-14 d (Dose adjusted with other parameters) (*n* = 23)	Graft function improved in 19 cases (83%)	1 death	9 infections (3 pulmonary aspergillosis, 2 CMV, 4 pulmonary/urinary bacterial infections)
7	Kainz *et al* [33], 2009	Retrospective, non-randomised, multi centre, Austria	N/A *n* = 399 (368 ATG, 31 OKT3)	Median actual graft survival 9.5 yr ATG *vs* 4.5 yr OKT3	N/A	N/A
8	van der Zwan *et al* [38], 2018	Retrospective, non-randomised, single centre, Netherlands	rATG – 4 mg/kg repeated after 4 d if CD3 > 200, for 2 wk (*n* = 103)	Median allograft survival 7.0 yr. At one yr 78.2% had functioning graft; At 5 yr 55.6% functioning graft; 49 lost graft in median f/u 6.8 yr	17 deaths	97 bacterial, 8 fungal, 27 CMV reactivation, 4 EBV reactivation, 6 BK viraemia), 14 malignancy (12 solid, 2 lymphoma)

ATG: Anti-thymocyte globulin; EBV: Epstein-Bar virus, CMV: Cytomegalovirus, rATG: Rabbit anti-thymocyte globulin; OKT3: Muromonab CD3, UTI: Urinary tract infection; N/A: Not applicable.

DISCUSSION

Despite the advancement of immunosuppressant therapy, AR remains one of the major problems in the field of clinical renal transplantation. The current approach in the management of acute kidney rejection in adults and children is based on the 2009 KDIGO guidelines[29]. These guidelines recommend corticosteroids for the initial treatment of acute cellular rejection. They advise adding or restoring maintenance prednisone in patients with rejection episodes who are not on steroids. They also recommend using lymphocyte-depleting agent or muromonab-CD3 (OKT3) for TCMR that does not respond to corticosteroids and for recurrent acute cellular rejections. The lymphocyte-depleting agent ATG has been used extensively for treating and preventing AR in kidney transplant recipients[21]. ATG has also been used as first-line therapy for those with severe acute TCMR including vascular lesions (Banff II or higher categories), and as rescue therapy for steroid-resistant acute TCMR (Tables 1 and 2). It has been shown that steroid-resistant rejection can be a significant problem in patients immunosuppressed with triple therapy (combination of tacrolimus [Tac], mycophenolate mofetil [MMF], and steroids) and 70% of such rejections can be reversed following ATG treatment[30]. A systemic review by Webster *et al*[23] was one of the comprehensive studies describing the advantages of using ATG over steroids for the treatment of steroid-resistant rejection. They studied 21 trials (49 reports, 1394 randomised participants) and concluded that in treating first rejection, ATG was superior to steroids in reversing rejection (relative risk [RR] = 0.57; 95% confidence interval [CI]: 0.38-0.87) and preventing graft loss (death-censored RR = 0.74; 95%CI: 0.58-0.95). However, there

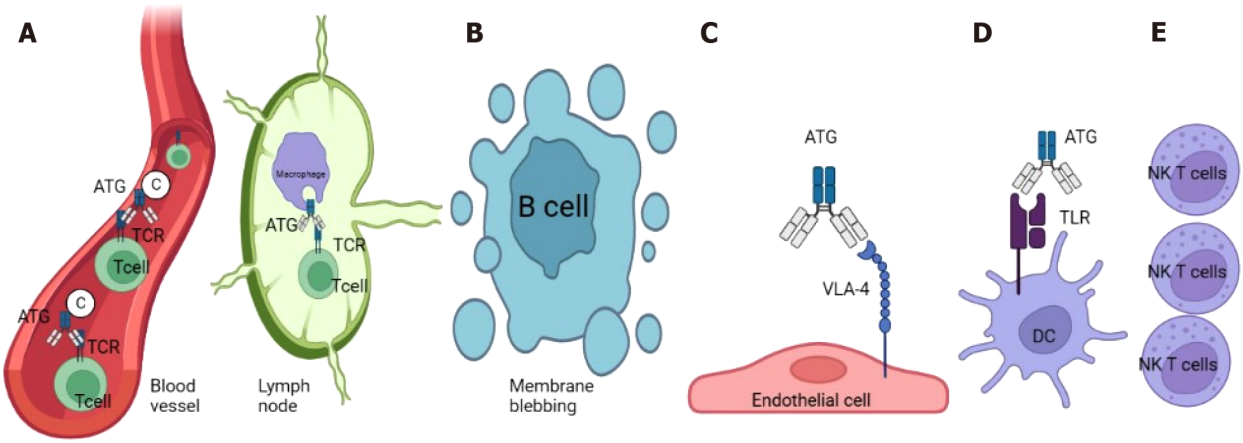

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Figure 1 Mechanisms of action of anti-thymocyte globulin. A: T-cell depletion in blood through complement-mediated lysis and in secondary lymphoid tissue by T cell apoptosis; B: B-cell apoptosis by anti-thymocyte globulin (ATG); C: ATG-VLA-4 complex leading to decreased adhesion proteins in endothelial cells required by leukocyte/endothelium interaction; D: Dendritic cell maturation by HLA1/ATG interaction; E: Increased natural killer T cells.

was no difference in preventing subsequent rejections (RR = 0.67; 95%CI: 0.43-1.04) or death (RR = 1.16; 95%CI: 0.57-2.33) at 1 year between ATG and steroids. Additionally, they also found no benefits with the use of muromonab-CD3 over ATG or ALG in reversing rejection, preventing subsequent rejection, or preventing graft loss or death. A decade later, in 2017[21], Webster *et al*[23] updated the review with 11 new trials (76 reports, 1680 participants). The updated meta-review concluded that antibody therapy was still better than steroid therapy (RR = 0.50; 95%CI: 0.30 to 0.82) for reversing the first acute rejection and preventing subsequent rejections (RR = 0.70; 95%CI: 0.50 to 0.99) and tended to help prevent graft loss (death-censored RR = 0.80; 95%CI: 0.57 to 1.12). There was no benefit of muromonab-CD3 over ATG in reversing rejection, preventing subsequent rejection, or preventing graft loss or death[29].

Muromonab-CD3 (Orthoclone, OKT3) is the first monoclonal antibody used clinically for immunosuppression. It eliminates CD3+ T cells from the peripheral circulation to produce the immunosuppressive effects. A few noticeable studies compared muromonab-CD3 with monoclonal and polyclonal antibodies in the treatment of steroid-resistant rejection[31,32]. Using clinical records stored in the Austrian Dialysis and Transplant Registry, Kainz *et al*[33] conducted a retrospective descriptive analysis of 399 (368 ATG treated *vs* 31 OKT3 treated) patients diagnosed with biopsy-confirmed acute rejection between 1990 to 2005. Their study suggested that ATG treatment for rejecting allograft exhibited longer graft survival over OKT3 treatment (median graft survival 9.5 years in ATG group *vs* 4.6 years in OKT3 group) and increased risk of graft loss in OKT3 group (hazard ratio = 1.73; 95%CI: 1.09-2.74; P = 0.019). ATG was better tolerated compared to OKT3, with a lower frequency of cytokine release syndrome.

Clinicians all around the world have backed studies to find a better alternative or newer, safer but more effective immunosuppressive regimen. Due to cost-effectiveness, adverse infusion reaction, prolonged duration of inpatient stay, and need for central venous access for ATG, Alemtuzumab (CD52-specific monoclonal antibody), which can be given subcutaneously in a single dose, has been put forward with some promising results. A propensity-matched controlled study of 116 patients treated with Alemtuzumab, in comparison to 108 patients treated with ATG, showed similar patient and allograft survival[26] whilst having superior infection-free survival with Alemtuzumab. The authors suggested that Alemtuzumab therapy may therefore be an alternative therapy for glucocorticoid-resistant, recurrent, or severe acute kidney transplant rejection.Registry data show that the incidence of AR has been steadily falling. The rate of AR used to be more than 50% in the 1970s, which has markedly dropped to 10%-20% today as per the United States, Australian, and New Zealand registries[2]. This can be attributed to the improvement of induction and maintenance of the immunosuppressive regimen. During the 1980s, the triple therapy regimen, which was the combination of low-dose cyclosporine, azathioprine, and prednisolone, was prescribed for maintenance immunosuppression[34,35]. Over the years, various combinations have been tried to find the optimal regimes. As of today, the best results overall are achieved with Tac, MMF, and steroids. A randomised trial conducted by Gonwa *et al*[36] demonstrated that this triple therapy regimen showed overall better outcomes in terms of graft and patient survival compared to other drug combinations. The study also showed that this combination provided particular benefits to kidney allograft recipients who develop delayed graft function/acute tubular necrosis. The landmark Symphony trial consolidated evidence for reduced exposure to calcineurin inhibitors in kidney transplantation, in conjunction with induction with daclizumab, MMF, and corticosteroids[37]. van der Zwan *et al*[38] recently showed the long-term outcome of the use of rATG with the combination of Tac + MMF + steroids for the treatment of AR. They concluded that early detection of AR followed by Tac + MMF + steroids with ATG provides better allograft functioning and survival. Survival after rATG was comparable to the overall survival of all kidney transplantation patients (P = 0.10).

However, there is a paucity of studies using ATG in current immunosuppression era and contemporary classification of AR. Only few studies in Tables 1 and 2 used Banff classification in the description of AR and when used, was from earlier classifications[39], at which point the role of antibody mediated component was less well understood.

The ATG dosage and duration varied widely among randomised studies as well as cohort studies described in Tables 1 and 2. The optimal dosing schedule in patients at high or low immunological risk has yet to be determined. Préville *et al* [40] derived data from a non-human primate model (cynomolgus monkey) which suggested that T-cell depletion with rATG is dose-dependent and that the optimal total dose required to achieve lymphocyte depletion in both peripheral blood and secondary lymphoid tissues (spleen and lymph nodes) is approximately 6.4 mg/kg. About 40% of patients treated with Thymoglobulin (mean of 6 doses at 1.5 mg/kg/d) have a recovery of > 50% of the initial lymphocyte count at 3 mo. Yet, time to immune reconstitution is characterized by not only a high intra-individual variability in the immune cell subpopulations (T and B cells, NK cells, DCs) but also an interindividual variability leading to prolonged lymphopenia for some patients up to 5 years[8]. When used as induction agent, a significant difference in infection rates was reported with rATG dose of < 7 mg/kg compared to use of > 7 mg/kg[41,42]. Since then, other studies have attempted to use the lower dose while optimizing the immunosuppressive effects of ATG[43,44]. However, in the context of AR treatment, guidance for use of ATG at 1.5 mg/kg remains broad at 7-14 d. It is difficult to pre-determine precise duration based on published studies. Variation in effects with intermittent dosing and continuous dosing was also reported (Tables 1 and 2). For CD3 count (T cells) < 200, 4 mg/kg bolus dose was used followed by re-dosing after 4 d, and for CD-3 count < 50[45], ATG was limited to 5 doses[46].

There is a need for further studies to unravel implications of ATG in treatment of rejections. These include: (1) Identifying patients most likely to benefit from ATG therapy. Clinical risk factors and kidney biopsy findings will need to be tested as a multivariate prediction model in determining outcomes that would enable choice of right patients; (2) It is possible that some of the intra-graft mRNA expression profiles (immune and non-immune biomarkers) could predict response to pulse glucocorticoid therapy in transplant recipients and likewise additional therapy to ATG[47]; (3) Evaluating benefit of ATG in late rejections compared to its benefit in treating early rejections; (4) Finding the optimal balance of immunosuppression in renal allograft recipients. Suboptimal immunosuppression can lead to rejection while over-immunosuppression can lead to life-threatening post-transplant infections. There remains no precise way to monitor the intensity of immunosuppression to prevent infectious complications[21]. Reports of CMV infection (Tables 1 and 2) were considerably high in published studies and prophylactic treatment with Valganciclovir for 3-6 mo is common practice lately; (5) Role of Torque-Teno Virus measurement (as a biomarker of immunosuppression to predict over/under-immunosuppression) is still in an infantile state[48]; (6) Role of ATG treatment in rejections due to non-compliance with maintenance immunosuppression medications. Currently, outcomes of treatment of such rejections is unclear; and (7) Role of anti-ATG antibodies in negating therapeutic potency of ATG needs to be established[49].

CONCLUSION

In conclusion, ATG emerges as a valuable therapeutic option for managing acute T-cell-mediated rejections, particularly in cases refractory to steroid treatment or characterized by higher grade rejections, such as Banff II or III. While the established standard dosing regimen recommends 1.5 mg/kg for a duration spanning 7 to 14 d, it is imperative to underscore the complexity of tailoring ATG therapy to individual patients, where striking the optimal balance between risks and benefits remains a formidable clinical challenge. To further advance our comprehension of this crucial treatment approach, it is imperative that we embark on comprehensive investigations. Large-scale studies, ideally based on registries, should be conducted with meticulous phenotyping of transplant recipients and thorough analysis of renal transplant biopsy characteristics. Such endeavours are indispensable in augmenting the existing body of scientific knowledge, ultimately enabling us to address the pertinent questions surrounding the precise use of ATG in the management of acute T-cell mediated rejections.

FOOTNOTES

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REFERENCES

1 **Hart A**, Smith JM, Skeans MA, Gustafson SK, Wilk AR, Robinson A, Wainright JL, Haynes CR, Snyder JJ, Kasiske BL, Israni AK. OPTN/SRTR 2016 Annual Data Report: Kidney. *Am J Transplant* 2018; **18** Suppl 1: 18-113 [PMID: 29292608 DOI: 10.1111/ajt.14557]

2 **Clayton PA**, McDonald SP, Russ GR, Chadban SJ. Long-Term Outcomes after Acute Rejection in Kidney Transplant Recipients: An ANZDATA Analysis. *J Am Soc Nephrol* 2019; **30**: 1697-1707 [PMID: 31308074 DOI: 10.1681/ASN.2018111101]

3 **Loupy A**, Haas M, Roufosse C, Naesens M, Adam B, Afrouzian M, Akalin E, Alachkar N, Bagnasco S, Becker JU, Cornell LD, Clahsen-van Groningen MC, Demetris AJ, Dragun D, Duong van Huyen JP, Farris AB, Fogo AB, Gibson IW, Glotz D, Gueguen J, Kikic Z, Kozakowski N, Kraus E, Lefaucheur C, Liapis H, Mannon RB, Montgomery RA, Nankivell BJ, Nickeleit V, Nickerson P, Rabant M, Racusen L, Randhawa P, Robin B, Rosales IA, Sapir-Pichhadze R, Schinstock CA, Seron D, Singh HK, Smith RN, Stegall MD, Zeevi A, Solez K, Colvin RB, Mengel M. The Banff 2019 Kidney Meeting Report (I): Updates on and clarification of criteria for T cell- and antibody-mediated rejection. *Am J Transplant* 2020; **20**: 2318-2331 [PMID: 32463180 DOI: 10.1111/ajt.15898]

4 **Rekers NV**, de Fijter JW, Claas FH, Eikmans M. Mechanisms and risk assessment of steroid resistance in acute kidney transplant rejection. *Transpl Immunol* 2016; **38**: 3-14 [PMID: 27480047 DOI: 10.1016/j.trim.2016.07.005]

5 **Thiyagarajan UM**, Ponnuswamy A, Bagul A. Thymoglobulin and its use in renal transplantation: a review. *Am J Nephrol* 2013; **37**: 586-601 [PMID: 23774740 DOI: 10.1159/000351643]

6 **Chapman JR**. The KDIGO clinical practice guidelines for the care of kidney transplant recipients. *Transplantation* 2010; **89**: 644-645 [PMID: 20164816 DOI: 10.1097/TP.0b013e3181d62f1b]

7 **Baker R**, Jardine A, Andrews P. Renal Association Clinical Practice Guideline on post-operative care of the kidney transplant recipient. *Nephron Clin Pract* 2011; **118** Suppl 1: c311-c347 [PMID: 21555902 DOI: 10.1159/000328074]

8 **Bamoulid J**, Staeck O, Crépin T, Halleck F, Saas P, Brakemeier S, Ducloux D, Budde K. Anti-thymocyte globulins in kidney transplantation: focus on current indications and long-term immunological side effects. *Nephrol Dial Transplant* 2017; **32**: 1601-1608 [PMID: 27798202 DOI: 10.1093/ndt/gfw368]

9 **Mohty M**. Mechanisms of action of antithymocyte globulin: T-cell depletion and beyond. *Leukemia* 2007; **21**: 1387-1394 [PMID: 17410187 DOI: 10.1038/sj.leu.2404683]

10 **Gaber AO**, Monaco AP, Russell JA, Lebranchu Y, Mohty M. Rabbit antithymocyte globulin (thymoglobulin): 25 years and new frontiers in solid organ transplantation and haematology. *Drugs* 2010; **70**: 691-732 [PMID: 20394456 DOI: 10.2165/11315940-000000000-00000]

11 **Genestier L**, Fournel S, Flacher M, Assossou O, Revillard JP, Bonnefoy-Berard N. Induction of Fas (Apo-1, CD95)-mediated apoptosis of activated lymphocytes by polyclonal antithymocyte globulins. *Blood* 1998; **91**: 2360-2368 [PMID: 9516135]

12 **Michallet MC**, Preville X, Flacher M, Fournel S, Genestier L, Revillard JP. Functional antibodies to leukocyte adhesion molecules in antithymocyte globulins. *Transplantation* 2003; **75**: 657-662 [PMID: 12640305 DOI: 10.1097/01.TP.0000053198.99206.E6]

13 **Monti P**, Allavena P, Di Carlo V, Piemonti L. Effects of anti-lymphocytes and anti-thymocytes globulin on human dendritic cells. *Int Immunopharmacol* 2003; **3**: 189-196 [PMID: 12586600 DOI: 10.1016/s1567-5769(02)00253-9]

14 **Gillet-Hladky S**, de Carvalho CM, Bernaud J, Bendahou C, Bloy C, Rigal D. Rabbit antithymocyte globulin inhibits monocyte-derived dendritic cells maturation in vitro and polarizes monocyte-derived dendritic cells towards tolerogenic dendritic cells expressing indoleamine 2,3-dioxygenase. *Transplantation* 2006; **82**: 965-974 [PMID: 17038913 DOI: 10.1097/01.tp.0000235549.47976.d0]

15 **Fang L**, Fehse B, Engel M, Zander A, Kröger N. Antithymocyte globulin induces ex vivo and in vivo depletion of myeloid and plasmacytoid dendritic cells. *Transplantation* 2005; **79**: 369-371 [PMID: 15699773 DOI: 10.1097/01.tp.0000150210.77543.1b]

16 **Lim HW**, Hillsamer P, Banham AH, Kim CH. Cutting edge: direct suppression of B cells by CD4+ CD25+ regulatory T cells. *J Immunol* 2005; **175**: 4180-4183 [PMID: 16177055 DOI: 10.4049/jimmunol.175.7.4180]

17 **Azuma T**, Takahashi T, Kunisato A, Kitamura T, Hirai H. Human CD4+ CD25+ regulatory T cells suppress NKT cell functions. *Cancer Res* 2003; **63**: 4516-4520 [PMID: 12907625]

18 **Chen W**. Dendritic cells and (CD4+)CD25+ T regulatory cells: crosstalk between two professionals in immunity versus tolerance. *Front Biosci* 2006; **11**: 1360-1370 [PMID: 16368522 DOI: 10.2741/1889]

19 **Brennan DC**, Daller JA, Lake KD, Cibrik D, Del Castillo D; Thymoglobulin Induction Study Group. Rabbit antithymocyte globulin versus basiliximab in renal transplantation. *N Engl J Med* 2006; **355**: 1967-1977 [PMID: 17093248 DOI: 10.1056/NEJMoa060068]

20 **Zapf A**, Gwinner W, Karch A, Metzger J, Haller H, Koch A. Non-invasive diagnosis of acute rejection in renal transplant patients using mass spectrometry of urine samples - a multicentre phase 3 diagnostic accuracy study. *BMC Nephrol* 2015; **16**: 153 [PMID: 26374548 DOI: 10.1186/s12882-015-0146-x]

21 **Webster AC**, Wu S, Tallapragada K, Park MY, Chapman JR, Carr SJ. Polyclonal and monoclonal antibodies for treating acute rejection episodes in kidney transplant recipients. *Cochrane Database Syst Rev* 2017; **7**: CD004756 [PMID: 28731207 DOI: 10.1002/14651858.CD004756.pub4]

22 **Wu K**, Budde K, Lu H, Schmidt D, Liefeldt L, Glander P, Neumayer HH, Rudolph B. The severity of acute cellular rejection defined by Banff classification is associated with kidney allograft outcomes. *Transplantation* 2014; **97**: 1146-1154 [PMID: 24892962 DOI: 10.1097/01.TP.0000441094.32217.05]

23 **Webster AC**, Pankhurst T, Rinaldi F, Chapman JR, Craig JC. Monoclonal and polyclonal antibody therapy for treating acute rejection in kidney transplant recipients: a systematic review of randomized trial data. *Transplantation* 2006; **81**: 953-965 [PMID: 16612264 DOI: 10.1097/01.tp.0000215178.72344.9d]

24 **Cooper JE**. Evaluation and Treatment of Acute Rejection in Kidney Allografts. *Clin J Am Soc Nephrol* 2020; **15**: 430-438 [PMID: 32066593 DOI: 10.2215/CJN.11991019]

25 **Luke PP**, Scantlebury VP, Jordan ML, Vivas CA, Hakala TR, Jain A, Somani A, Fedorek S, Randhawa P, Shapiro R. Reversal of steroid- and anti-lymphocyte antibody-resistant rejection using intravenous immunoglobulin (IVIG) in renal transplant recipients. *Transplantation* 2001; **72**: 419-422 [PMID: 11502969 DOI: 10.1097/00007890-200108150-00010]

26 **van der Zwan M**, Clahsen-Van Groningen MC, van den Hoogen MWF, Kho MML, Roodnat JI, Mauff KAL, Roelen DL, van Agteren M, Baan CC, Hesselink DA. Comparison of Alemtuzumab and Anti-thymocyte Globulin Treatment for Acute Kidney Allograft Rejection. *Front Immunol* 2020; **11**: 1332 [PMID: 32719676 DOI: 10.3389/fimmu.2020.01332]

27 **Eikmans M**, Roelen DL, Claas FH. Molecular monitoring for rejection and graft outcome in kidney transplantation. *Expert Opin Med Diagn* 2008; **2**: 1365-1379 [PMID: 23496783 DOI: 10.1517/17530050802600683]

28 **Shinn C**, Malhotra D, Chan L, Cosby RL, Shapiro JI. Time course of response to pulse methylprednisolone therapy in renal transplant recipients with acute allograft rejection. *Am J Kidney Dis* 1999; **34**: 304-307 [PMID: 10430978 DOI: 10.1016/s0272-6386(99)70359-8]

29 **Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group**. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant* 2009; **9** Suppl 3: S1-155 [PMID: 19845597 DOI: 10.1111/j.1600-6143.2009.02834.x]

30 **Richardson AJ**, Higgins RM, Liddington M, Murie J, Ting A, Morris PJ. Antithymocyte globulin for steroid resistant rejection in renal transplant recipients immunosuppressed with triple therapy. *Transpl Int* 1989; **2**: 27-32 [PMID: 2669801 DOI: 10.1007/BF02425968]

31 **Mariat C**, Alamartine E, Diab N, de Filippis JP, Laurent B, Berthoux F. A randomized prospective study comparing low-dose OKT3 to low-dose ATG for the treatment of acute steroid-resistant rejection episodes in kidney transplant recipients. *Transpl Int* 1998; **11**: 231-236 [PMID: 9638854 DOI: 10.1007/s001470050133]

32 **Casadei DH**, del C Rial M, Opelz G, Golberg JC, Argento JA, Greco G, Guardia OE, Haas E, Raimondi EH. A randomized and prospective study comparing treatment with high-dose intravenous immunoglobulin with monoclonal antibodies for rescue of kidney grafts with steroid-resistant rejection. *Transplantation* 2001; **71**: 53-58 [PMID: 11211195 DOI: 10.1097/00007890-200101150-00009]

33 **Kainz A**, Korbély R, Soleiman A, Mayer B, Oberbauer R. Antithymocyte globulin use for treatment of biopsy confirmed acute rejection is associated with prolonged renal allograft survival. *Transpl Int* 2010; **23**: 64-70 [PMID: 19719467 DOI: 10.1111/j.1432-2277.2009.00950.x]

34 **Amenábar JJ**, Gómez-Ullate P, García-López FJ, Aurrecoechea B, García-Erauzkin G, Lampreabe I. A randomized trial comparing cyclosporine and steroids with cyclosporine, azathioprine, and steroids in cadaveric renal transplantation. *Transplantation* 1998; **65**: 653-661 [PMID: 9521199 DOI: 10.1097/00007890-199803150-00009]

35 **Jones RM**, Murie JA, Allen RD, Ting A, Morris PJ. Triple therapy in cadaver renal transplantation. *Br J Surg* 1988; **75**: 4-8 [PMID: 3276369 DOI: 10.1002/bjs.1800750104]

36 **Gonwa T**, Johnson C, Ahsan N, Alfrey EJ, Halloran P, Stegall M, Hardy M, Metzger R, Shield C 3rd, Rocher L, Scandling J, Sorensen J, Mulloy L, Light J, Corwin C, Danovitch G, Wachs M, VanVeldhuisen P, Leonhardt M, Fitzsimmons WE. Randomized trial of tacrolimus + mycophenolate mofetil or azathioprine versus cyclosporine + mycophenolate mofetil after cadaveric kidney transplantation: results at three years. *Transplantation* 2003; **75**: 2048-2053 [PMID: 12829910 DOI: 10.1097/01.TP.0000069831.76067.22]

37 **Ekberg H**, Tedesco-Silva H, Demirbas A, Vítko S, Nashan B, Gürkan A, Margreiter R, Hugo C, Grinyó JM, Frei U, Vanrenterghem Y, Daloze P, Halloran PF; ELITE-Symphony Study. Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med* 2007; **357**: 2562-2575 [PMID: 18094377 DOI: 10.1056/NEJMoa067411]

38 **van der Zwan M**, Clahsen-Van Groningen MC, Roodnat JI, Bouvy AP, Slachmuylders CL, Weimar W, Baan CC, Hesselink DA, Kho MML. The Efficacy of Rabbit Anti-Thymocyte Globulin for Acute Kidney Transplant Rejection in Patients Using Calcineurin Inhibitor and Mycophenolate Mofetil-Based Immunosuppressive Therapy. *Ann Transplant* 2018; **23**: 577-590 [PMID: 30115901 DOI: 10.12659/AOT.909646]

39 **Solez K**, Axelsen RA, Benediktsson H, Burdick JF, Cohen AH, Colvin RB, Croker BP, Droz D, Dunnill MS, Halloran PF. International standardization of criteria for the histologic diagnosis of renal allograft rejection: the Banff working classification of kidney transplant pathology. *Kidney Int* 1993; **44**: 411-422 [PMID: 8377384 DOI: 10.1038/ki.1993.259]

40 **Préville X**, Flacher M, LeMauff B, Beauchard S, Davelu P, Tiollier J, Revillard JP. Mechanisms involved in antithymocyte globulin immunosuppressive activity in a nonhuman primate model. *Transplantation* 2001; **71**: 460-468 [PMID: 11233911 DOI: 10.1097/00007890-200102150-00021]

41 **Clesca P**, Dirlando M, Park SI, García R, Ferraz E, Pinheiro-Machado PG, Kushnaroff L, Tedesco-Silva H Jr, Medina-Pestana JO. Thymoglobulin and rate of infectious complications after transplantation. *Transplant Proc* 2007; **39**: 463-464 [PMID: 17362760 DOI: 10.1016/j.transproceed.2007.01.024]

42 **Laftavi MR**, Patel S, Soliman MR, Alnimri M, Kohli R, Said M, Pankewycz O. Low-dose thymoglobulin use in elderly renal transplant recipients is safe and effective induction therapy. *Transplant Proc* 2011; **43**: 466-468 [PMID: 21440735 DOI: 10.1016/j.transproceed.2011.01.039]

43 **Agha IA**, Rueda J, Alvarez A, Singer GG, Miller BW, Flavin K, Lowell JA, Shenoy S, Howard TK, Ramachandran V, Irish W, Schnitzle MA, Brennan DC. Short course induction immunosuppression with thymoglobulin for renal transplant recipients. *Transplantation* 2002; **73**: 473-475 [PMID: 11884948 DOI: 10.1097/00007890-200202150-00025]

44 **Peddi VR**, Bryant M, Roy-Chaudhury P, Woodle ES, First MR. Safety, efficacy, and cost analysis of thymoglobulin induction therapy with intermittent dosing based on CD3+ lymphocyte counts in kidney and kidney-pancreas transplant recipients. *Transplantation* 2002; **73**: 1514-1518 [PMID: 12023634 DOI: 10.1097/00007890-200205150-00025]

45 **Clark KR**, Forsythe JL, Shenton BK, Lennard TW, Proud G, Taylor RM. Administration of ATG according to the absolute T lymphocyte count during therapy for steroid-resistant rejection. *Transpl Int* 1993; **6**: 18-21 [PMID: 8383974 DOI: 10.1007/BF00336633]

46 **Sharma RK**, Kumar A, Kumar J, Gupta A, Gulati S, Sharma AP, Bhandari M. Low-dose ATG is effective in treatment of acute rejection episodes. *Transplant Proc* 2003; **35**: 225-226 [PMID: 12591374 DOI: 10.1016/s0041-1345(02)03895-2]

47 **Tai E**, Chapman JR. The KDIGO review of the care of renal transplant recipient. *Pol Arch Med Wewn* 2010; **120**: 237-242 [PMID: 20567208 DOI: 10.20452/pamw.935]

48 **Rezahosseini O**, Drabe CH, Sørensen SS, Rasmussen A, Perch M, Ostrowski SR, Nielsen SD. Torque-Teno virus viral load as a potential endogenous marker of immune function in solid organ transplantation. *Transplant Rev (Orlando)* 2019; **33**: 137-144 [PMID: 30981537 DOI: 10.1016/j.trre.2019.03.004]

49 **Pascual J**, Zuckermann A, Djamali A, Hertig A, Naesens M. Rabbit antithymocyte globulin and donor-specific antibodies in kidney transplantation--A review. *Transplant Rev (Orlando)* 2016; **30**: 85-91 [PMID: 26951711 DOI: 10.1016/j.trre.2015.12.002]

50 **Shield CF 3rd**, Cosimi AB, Tolkoff-Rubin N, Rubin RH, Herrin J, Russell PS. Use of antithymocyte globulin for reversal of acute allograft rejection. *Transplantation* 1979; **28**: 461-464 [PMID: 390784 DOI: 10.1097/00007890-197912000-00005]

51 **Filo RS**, Smith EJ, Leapman SB. Therapy of acute cadaveric renal allograft rejection with adjunctive antithymocyte globulin. *Transplantation* 1980; **30**: 445-449 [PMID: 7008293 DOI: 10.1097/00007890-198012000-00012]

52 **Hoitsma AJ**, Reekers P, Kreeftenberg JG, van Lier HJ, Capel PJ, Koene RA. Treatment of acute rejection of cadaveric renal allografts with rabbit antithymocyte globulin. *Transplantation* 1982; **33**: 12-16 [PMID: 7039017 DOI: 10.1097/00007890-198201000-00003]

53 **Toledo-Pereyra LH**, Bergren C, Mittal VK, Whitten JI, Baskin S, McNichol L. A prospective randomized comparison of antilymphoblast globulin versus antithymocyte globulin for cadaver kidney transplantation. *Transplantation* 1985; **40**: 448-450 [PMID: 3901446]

54 **Alamartine E**, Bellakoul R, Berthoux F. Randomized prospective study comparing OKT3 and antithymocyte globulins for treatment of the first acute cellular rejection of kidney allografts. *Transplant Proc* 1994; **26**: 273-274 [PMID: 8108975]

55 **Tesi RJ**, Kano JM, Horn HR, Schroeder T. Thymoglobulin reverses acute renal allograft rejection better than ATGAM--a double-blinded randomized clinical trial. *Transplant Proc* 1997; **29**: 21S-23S [PMID: 9366922]

56 **Gaber AO**, First MR, Tesi RJ, Gaston RS, Mendez R, Mulloy LL, Light JA, Gaber LW, Squiers E, Taylor RJ, Neylan JF, Steiner RW, Knechtle S, Norman DJ, Shihab F, Basadonna G, Brennan DC, Hodge EE, Kahan BD, Kahan L, Steinberg S, Woodle ES, Chan L, Ham JM, Schroeder TJ. Results of the double-blind, randomized, multicenter, phase III clinical trial of Thymoglobulin versus Atgam in the treatment of acute graft rejection episodes after renal transplantation. *Transplantation* 1998; **66**: 29-37 [PMID: 9679818 DOI: 10.1097/00007890-199807150-00005]

57 **Theodorakis J**, Schneeberger H, Illner WD, Stangl M, Zanker B, Land W. Aggressive treatment of the first acute rejection episode using first-line anti-lymphocytic preparation reduces further acute rejection episodes after human kidney transplantation. *Transpl Int* 1998; **11** Suppl 1: S86-S89 [PMID: 9664951 DOI: 10.1007/s001470050433]

58 **Baldi A**, Malaise J, Mourad M, Squifflet JP. A prospective randomized study comparing poly-ATG to mono-OKT3 clonal antibodies for the first rejection therapy after kidney transplantation: long-term results. *Transplant Proc* 2000; **32**: 429-431 [PMID: 10715467 DOI: 10.1016/s0041-1345(00)00838-1]

59 **Midtvedt K**, Fauchald P, Lien B, Hartmann A, Albrechtsen D, Bjerkely BL, Leivestad T, Brekke IB. Individualized T cell monitored administration of ATG versus OKT3 in steroid-resistant kidney graft rejection. *Clin Transplant* 2003; **17**: 69-74 [PMID: 12588325 DOI: 10.1034/j.1399-0012.2003.02105.x]

60 **Hardy MA**, Nowygrod R, Elberg A, Appel G. Use of ATG in treatment of steroid-resistant rejection. *Transplantation* 1980; **29**: 162-164 [PMID: 6986690 DOI: 10.1097/00007890-198002000-00015]

61 **Uslu A**, Tokat Y, Ok E, Unsal A, Ilkgul O, Kaplan H. ATG versus OKT3 in the treatment of steroid-resistant rejection following living-related donor renal transplantation. *Transplant Proc* 1997; **29**: 2805-2806 [PMID: 9365571 DOI: 10.1016/s0041-1345(97)00686-6]

62 **Colak T**, Sevmiş S, Karakayali H, Moray G, Haberal M. One center's experience with antithymocyte globulin treatment for acute rejection in renal transplantation. *Transplant Proc* 2008; **40**: 123-125 [PMID: 18261564 DOI: 10.1016/j.transproceed.2007.12.008]

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