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R E V I E W

Rabbit Anti-Thymocyte Globulin: Evidence for Clinical Benefit in High Immunological Risk Kidney Transplantation

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Abstract: Rabbit anti-thymocyte globulin is used worldwide to treat and prevent rejection in kidney transplantation. Multiple mechanisms of action of this polyclonal preparation are responsible for its success. Studies have supported clinical benefits of rabbit anti-thymocyte globulin in high immunological risk kidney transplant recipients when used as an induction agent at the time of transplant and for treatment of rejection when compared to other antibody therapy. The evidence of this clinical benefit will be reviewed in addition to examining the dosing and safety profile of rabbit anti-thymocyte globulin.

Keywords: Rabbit anti-thymocyte globulin, kidney transplantation, high immunological risk

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Introduction
Transplantation of high immunological risk kidney transplant recipients presents unique challenges, and rabbit anti-thymocyte globulin has been effectively used in this population. Rabbit anti-thymocyte globulins have a proven track record in treating recipients of kidney transplantation since 1984. Thymoglobulin®, a rabbit anti-thymocyte globulin (rATG) made from human thymocytes subsequently became available in the United States in 1998 for use in treating acute rejection. An alternative rabbit anti-thymocyte globulin, ATG-Fresenius S®, uses cultured Jurkat cells, an immortalized line of T cells, as the immunogen. The focus of this paper is on the use of Thymoglobulin®, the more widely used rATG.

Because of its effectiveness in treating rejection, rATG has been used off-label as an induction agent, particularly in those patients considered high immunological risk. Included in this group are patients undergoing retransplantation, those that are highly sensitized (including panel reactive antibody titers of ≥20% or the presence of a donor specific antibody), and African-American patients.1,2 rATG has become the most common induction agent used in the United States and has become the induction treatment of choice in high immunological risk patients.3–5 In exploring the evidence demonstrating clinical benefit of rATG in high immunological risk kidney transplantation, the mechanisms of action, use as induction, treatment for rejection, appropriate dose and safety will be reviewed.

Mechanisms of Action
The mechanisms of action of rATG appear to be many, and effects on T cell, B cell, plasma cell and regulatory cell lines in addition to lymphocyte adhesion and chemotaxis have been implicated. rATG is a purified, pasteurized preparation of rabbit immunoglobulin obtained by immunization against human thymocytes.6 Ninety percent of the immunoglobulin is IgG. Antibodies to CD2, CD3, CD4, CD8, CD11a, CD18, CD25, CD44, CD45, HLA-DR, HLA Class I heavy chain, beta 2 microglobulin are described in the package insert.6 Many other antibody specificities have been identified.7 A full discussion of the known mechanisms of action of rATG is beyond the scope of this paper and the reader is referred to some excellent reviews.7–13 A few important properties will be analyzed for this discussion. The primary effect of rATG is T cell inhibition and depletion through complement dependent cell lysis in the blood and apoptosis in the lymphoid tissue.7–9 Modulation of T cell receptors leaves the T cell hypo-responsive to stimuli and also inhibits T cell homing.7,14 This latter characteristic of inhibition of leukocyte adhesion via CD11a/LFA-1 in addition to blockade of leukocyte trafficking via T cell CXCR4/SDF-1α mediated chemotaxis may explain the decreased ischemia-reperfusion injury leading to less delayed graft function compared to other antibody preparations.14–16 Furthermore, rATG contains antibodies directed against platelets that may decrease tissue injury post ischemic insults.17,18 The unfraccionated human thymocytes used to generate the rabbit antibody response contain B cells, plasma cells and dentritic cells.19 Thus, rATG carries a number of specific antibodies to CD19, CD20, CD30, CD38, HLA-DR, CD124, and CD 138 and may be responsible for depletion of B cells and plasma cells through cell lysis and/or apoptosis (by way of caspase dependent, cathespin-B dependent or mitochondrial membrane depolarization).20 However, the effect of rATG on inhibiting memory B cells is mixed.8,20 There is no data that the plasma cell antibodies in rATG inhibit plasma cell activation (by way of caspase dependent, cathespin-B dependent or mitochondrial membrane depolarization).20,21 The unfractionated human thymocytes used to generate the rabbit antibody response contain B cells, plasma cells and dentritic cells.19 Thus, rATG carries a number of specific antibodies to CD19, CD20, CD30, CD38, HLA-DR, CD124, and CD 138 and may be responsible for depletion of B cells and plasma cells through cell lysis and/or apoptosis (by way of caspase dependent, cathespin-B dependent or mitochondrial membrane depolarization).20 However, the effect of rATG on inhibiting memory B cells is mixed.8,20 There is no data that the plasma cell antibodies in rATG inhibit plasma cell activation (by way of caspase dependent, cathespin-B dependent or mitochondrial membrane depolarization).20,21 The unfractionated human thymocytes used to generate the rabbit antibody response contain B cells, plasma cells and dentritic cells.19 Thus, rATG carries a number of specific antibodies to CD19, CD20, CD30, CD38, HLA-DR, CD124, and CD 138 and may be responsible for depletion of B cells and plasma cells through cell lysis and/or apoptosis (by way of caspase dependent, cathespin-B dependent or mitochondrial membrane depolarization).20 However, the effect of rATG on inhibiting memory B cells is mixed.8,20 There is no data that the plasma cell antibodies in rATG inhibit plasma cell activation (by way of caspase dependent, cathespin-B dependent or mitochondrial membrane depolarization).20,21 The unfractionated human thymocytes used to generate the rabbit antibody response contain B cells, plasma cells and dentritic cells.19 Thus, rATG carries a number of specific antibodies to CD19, CD20, CD30, CD38, HLA-DR, CD124, and CD 138 and may be responsible for depletion of B cells and plasma cells through cell lysis and/or apoptosis (by way of caspase dependent, cathespin-B dependent or mitochondrial membrane depolarization).20 However, the effect of rATG on inhibiting memory B cells is mixed.8,20 There is no data that the plasma cell antibodies in rATG inhibit plasma cell activation (by way of caspase dependent, cathespin-B dependent or mitochondrial membrane depolarization).20,21 The unfractionated human thymocytes used to generate the rabbit antibody response contain B cells, plasma cells and dentritic cells.19 Thus, rATG carries a number of specific antibodies to CD19, CD20, CD30, CD38, HLA-DR, CD124, and CD 138 and may be responsible for depletion of B cells and plasma cells through cell lysis and/or apoptosis (by way of caspase dependent, cathespin-B dependent or mitochondrial membrane depolarization).20 However, the effect of rATG on inhibiting memory B cells is mixed.8,20 There is no data that the plasma cell antibodies in rATG inhibit plasma cell activation (by way of caspase dependent, cathespin-B dependent or mitochondrial membrane depolarization).20,21

Induction
Trials using rATG as induction therapy in kidney transplantation to lower the risk of early rejection followed the successes of rATG in treating rejection episodes.26–29 The purpose of induction therapy is to reduce the incidence of rejection, a defined risk factor for graft loss.30,31 Achievement of excellent durable outcomes in low immunological risk patients accompanied by favorable long-term safety profiles saw subsequent use of rATG in high risk scenarios.26,32,33 We will review results of using rATG induction in high immunological risk kidney transplant recipients using rATG while on maintenance immunosuppression.25
with basiliximab, daclizumab, alemtuzumab and its use in African-Americans and crossmatch positive recipients.

**Induction: rATG Versus Basiliximab**

Basiliximab, an IL-2 receptor blocker, has been compared to rATG in high immunological risk patients. Brennan et al prospectively randomized 278 kidney transplant recipients at high risk for rejection or delayed graft function to receive rATG (1.5 mg/kg for 5 doses with the first dose given intra-operatively before reperfusion) versus basiliximab (20 mg on days 0 and 4) and compared outcome at 1 year.\(^3\) Maintenance therapy consisted of cyclosporine (modified), mycophenolate mofetil and corticosteroids. There were no differences in demographics between the groups. The primary end point was a composite of first biopsy proven rejection, delayed graft function, graft loss or death and there were no differences in patient characteristics between the groups. The rATG group had less rejection than the basiliximab group (15.5% versus 25.5%, \(P = 0.02\)) and the rejection rate numerically was lower among African-Americans and non-African-Americans in the rATG group. Severe rejection defined as the need for anti-thymocyte globulin therapy was lower in the rATG group (1.4% versus 8%, \(P = 0.005\)). The rate of delayed graft function, graft loss and death were not different between the groups. Brennan and Schnitzler analyzed 5 year outcomes of the United States participants in this international study.\(^3\) They collected data from the Organ Procurement and Transplantation Network registry to determine 5 year incidence of rejection and graft survival in the 183 U.S. participants. The baseline demographics did not differ between the U.S. patients receiving rATG and basiliximab. However, the 1 and 5 year rates of rejection were lower in the rATG group (15% versus 27%, \(P = 0.03\) and 3% versus 12%, \(P = 0.05\)), respectively. Less patients reached the composite end point in the rATG group at 5 years (37% versus 51%, \(P = 0.04\)).

Bunnapradist and Takamoto conducted a review of 24,901 transplants reported to the United Network of Organ Sharing database to analyze the patient characteristics of those receiving induction and the outcomes. Those receiving induction (rATG, basiliximab, daclizumab) were more likely to be pediatric recipients, sensitized (PRA > 30%), DR mismatched and using tacrolimus immunosuppression. The rATG group had higher incidences of kidney recipients that are sensitized, retransplanted or experienced delayed graft function. Although there were no differences in graft survival between the groups receiving induction at 2 years, those that got rATG had reduced risk for rejection (OR = 0.67 [0.59–0.77]).

Knight et al retrospectively looked at 145 kidney transplant recipients treated with rATG (n = 30) or basiliximab (n = 103) for induction.\(^3\) The patients were further stratified based on immunological risk, with high risk defined as African-American race, retransplants or PRA > 50%. The dose of the basiliximab was 20 mg on days 0 and 4. The rATG was given at a dose of 1.5 mg/kg on a daily basis until the creatinine fell to 2.5 mg/dl or lower (no more than 14 doses—mean 8 ± 4). The investigator determined if the rATG was started intra-operatively or on day 1. Maintenance immunosuppression included sirolimus, cyclosporine (modified) and corticosteroids. The high immunological risk rATG group had lower rate of rejection than the high immunological risk basiliximab group (3% versus 26%, \(P = 0.01\)). There was numerically less delayed graft function in the rATG group (7% versus 24%, \(P = NS\)). At 12 months, the rATG group had statistically better renal function with creatinine of 1.4 ± 0.6 versus 1.9 ± 0.8 mg/dl, \(P = 0.01\).

Cherikh et al mined the UNOS-OPTN database to report incidence of graft survival in those kidney transplant patients receiving no induction or various antibody preparations that included monoclonal, polyclonal and IL-2 receptor antibody.\(^3\) Demographics show higher rate of sensitization, higher incidence of delayed graft function, less use of tacrolimus or mycophenolate mofetil in the polyclonal anti-lymphocyte antibody group compared to the IL-2 receptor antibodies (IL-2Ra) group that was statistically significant. Follow-up was only 727 days, and IL-2Ra were associated with 17% (\(P = 0.002\)) lower risk of graft loss compared to no induction, but there were no differences in graft loss between the polyclonal anti-lymphocyte preparations and no induction. Neither the name of the polyclonal antibody nor the dose was mentioned in this paper.

Patolla et al evaluated the Scientific Registry of Transplant Recipients database to determine outcomes of those receiving no induction, IL-2Ra (basiliximab or daclizumab) versus anti-lymphocyte antibodies—ALA
(rATG, ALG, eATG, Nashville rATG or OKT3). Incidence of rejection was lower in both IL-2Ra and ALA groups at 6 and 12 months compared to the no induction group, and numerically less rejection occurred with the ALA compared to the IL-2Ra group. The graft survival between the groups was the same. No breakout of results for the individual ALA was provided and follow-up was short. An analysis by Webster et al of induction with no agents, placebo, IL-2Ra or other antibody therapy reached similar conclusions. Data was collected from 71 studies involving 10,520 patients. IL-2Ra use had a higher risk for biopsy-proven rejection than the ATG (rATG one of many) group at 1 year (RR 1.30 95% CI 1.01–1.67), but no difference in clinical rejection or graft survival were noted.

Augustine et al reviewed outcomes of transplants in 130 consecutive kidney or kidney/pancreas recipients, some treated with rATG or basiliximab induction and the others not. They retrospectively reviewed the results of interferon gamma ELISPOT assay—a marker of effector or memory T-cell alloreactivity. Induction was used in 32 patients, 24 receiving basiliximab and 8 rATG. Induction was chosen based on kidney-pancreas transplant, multicenter trial protocol, positive B cell crossmatch, and surgeon preference. Maintenance immunosuppression varied, but there was no statistical difference between the groups that were ELISPOT(+) and those that were ELISPOT(−). Rejection occurred in 34% of the ELISPOT(+) patients, but only 13% of the ELISPOT(−). Thirty-two of the 130 patients were ELISPOT(+), and of these, 5 received basiliximab and 3 were induced with rATG. No rejection was seen in the 8 ELISPOT(−) recipients undergoing induction, but 46% of the 24 ELISPOT(+) patients induction free suffered rejection (P = 0.02). There was no difference in the rejection rate of the ELISPOT(−) patients treated with induction or induction free (overall 13% rejection rate). Weaknesses of this study included its retrospective nature, diverse maintenance immunosuppression, and the elective nature of using induction. It supports the idea of induction therapy, including rATG, being beneficial in high immunological risk patients.

Induction: rATG Versus Alemtuzumab
Alemtuzumab and rATG have been compared head-to-head in varying immunological risk kidney and pancreas transplant patients with high risk defined as PRA > 20%, retransplants and African-Americans under 40 years old. The dose of the alemtuzumab was a single 30 mg dose, whereas the rATG was given 1.5 mg/kg on alternate days until creatinine fell by 50%. In almost all high risk patients, maintenance immunosuppression was tacrolimus, mycophenolate mofetil and corticosteroids. One hundred thirteen patients received alemtuzumab and 109 rATG. Enrollment of the kidney only patients was discontinued after 180 transplants because the incidence of biopsy-proven rejection was higher in the rATG group, 24% versus 12%, P = 0.03. Although numerically higher, there

Induction: rATG Versus Daclizumab
rATG has been directly compared to the other IL-2Ra, daclizumab, in high immunological risk kidney recipients. An abstract by Locke et al compared rATG and daclizumab in kidney patients with donor specific antibodies. It is not clear if the recipients received treatment to remove the DSA, nor is the dose of induction administered discussed. The incidence of rejection was lower in the rATG group, 67% versus 95% (P = 0.02). Interestingly, they report that numerically more of the patients undergoing daclizumab therapy lost the DSA (70% versus 52% in the rATG group, P = 0.2). Patient and graft survival were the same between groups. Noël et al studied 227 high immunological risk recipients defined by current PRA ≥ 30%, peak PRA ≥ 50%, loss of first kidney from rejection within 2 years of transplant or 2–3 previous kidneys. rATG was administered daily at 1.25 mg/kg for 8 doses. Daclizumab was given at 1 mg/kg on days 0, 14, 28, 42 and 56. Both were given intra-operatively before reperfusion of the graft. Maintenance immunosuppression used tacrolimus, mycophenolate mofetil and corticosteroids. The primary end point of biopsy-proven rejection occurred in 15% of the rATG group and 27% of the daclizumab treated recipients, P = 0.016. Delayed graft function developed in 32% of the rATG patients and 45% of the daclizumab group, P = 0.044. Patient and graft survival at 1 year were similar as was renal function. Longer follow-up would be needed to see if the lower rejection and delayed graft function rates translate into better graft survival. More data is needed to draw firm conclusions but these early results suggest benefit using rATG in high immunological risk patients.
was no statistical difference in rejection rates of the high risk patients, 29% versus 17% ($P = 0.1$) nor any difference in delayed graft function. Graft and patient survival were similar, but renal function at 2 years measured by estimated MDRD GFR was better in the alemtuzumab group, 58 $\pm$ 18 versus 45 $\pm$ 18 ml/min ($P = 0.04$). Others have reported results of induction using alemtuzumab and rATG, but the maintenance immunosuppression differed between groups making firm conclusions difficult.44–46

**Induction: rATG Use in African-Americans**

African-American race is considered a risk for rejection and decreased graft survival.47–49 rATG has been used to reduce rejection and improve graft survival in African-American kidney transplant recipients over other agents. Haririan et al retrospectively analyzed outcomes in 88 African-American kidney recipients receiving induction with rATG (36 patients) or basiliximab (52 patients).50 The dose of rATG was 1.5 mg/kg daily for 4–7 days and basiliximab was 20 mg on days 0 and 4. The rATG group had significantly more retransplants (44% versus 2%, $P < 0.0001$), more sensitization (current PRA $> 10\%$ in 47% versus 0%, $P < 0.0001$), and numerically more delayed graft function (50% versus 38%, $P = 0.21$). Maintenance immunosuppression included mycophenolate mofetil, corticosteroids and sirolimus for those with delayed graft function and tacrolimus for those without. During 19 months of follow-up, there was no statistical difference in graft survival, incidence of rejection, or creatinine between the induction groups. Fleming et al describe a review of 189 African-American kidney transplant patients that met the standard of low immunological risk, excluding those with PRA $> 20\%$, retransplants, B-cell positive crossmatch and individuals at high risk for delayed graft function.51 Forty-three of these were treated with rATG at the discretion of the attending physician, receiving 1.5 mg/kg for 5–9 days. The others used induction with basiliximab (20 mg on days 0 and 4) or daclizumab 1 mg/kg dosed on days 0 and 7. All received maintenance immunosuppression with a calcineurin inhibitor, mycophenolate mofetil and corticosteroids. No differences between the groups were found at one year for rejection (12% in each group), creatinine or graft survival. Haririan et al used rATG as induction to evaluate the effect of early steroid withdrawal (40 patients) versus control group (33 patients) with standard steroid use in African-American kidney transplant recipients on maintenance with mycophenolate mofetil and tacrolimus or sirolimus.52 The dose of rATG was 1.5 mg/kg daily for 4–11 days. There were no differences between the early steroid withdrawal group and those continuing chronic steroid usage with respect to incidence of rejection, graft survival, or estimated creatinine clearance. This supports the notion that modern immunosuppression may mitigate immunological risk in African-American recipients. Hammond et al retrospectively reviewed outcomes of 175 African-American kidney transplant recipients treated with no induction (n = 40), IL-2R antagonists (n = 81) and rATG (n = 54).53 For almost all patients, maintenance immunosuppression consisted of calcineurin inhibitors, mycophenolate mofetil and corticosteroids. There were no baseline differences in patient characteristics between the groups; however, the rATG group had significantly more retransplants (5% versus 3% versus 32%, $P < 0.001$) and more sensitized recipients with PRA $> 20\%$ (8% versus 15% versus 54%), respectively. Incidence of rejection at one year was 47% (no induction), 26% (IL-2R antagonists), and 18% (rATG) and 3 year graft survival was 66%, 85% and 76%, respectively, between the groups. No statistical difference was seen between the induction arms for 1 year rejection or 3 year graft survival. Each induction arm was statistically better at reducing 1 year rejection rates compared to no induction, but only the IL-2R antagonists had significantly better graft survival at 3 years compared to the no induction arm. It was difficult to draw firm conclusions between the induction arm outcomes because of the differences in immunological risk between the 2 groups. Graft loss and rejection rates are particularly high in African-Americans who undergo retransplantation.54,55 Gruber et al conducted a retrospective review of 140 first and 26 second kidney transplants in African-Americans to look at the effect of induction and modern immunosuppression on graft success in second transplants.56 The retransplant group had significantly higher number of recipients with PRA $> 10\%$ (69% versus 7%) and received more doses of rATG. Only 15% of retransplants were treated with early steroid withdrawal compared to 51% for primary transplants. rATG was induction in...
100% of the retransplants and 70% of the primary transplants (the other 30% received basiliximab). Graft survival, patient survival and creatinine were similar between the groups at one year supporting the idea that modern immunosuppression used with rATG induction and chronic corticosteroid in high immunological risk retransplants produces comparable rejection rates, graft survival and renal function to those undergoing primary transplant.

**Induction: rATG Use in Crossmatch Positive Recipients**

rATG has found a valuable role in reducing risk of rejection and graft loss in kidney transplantation in the presence of low level anti-donor HLA antibody. This low level antibody as defined by CDC-AHG negative, flow cytometry positive crossmatch is considered an intermediate risk for antibody mediated rejection. To reduce the risk of rejection and improve graft survival, rATG and intravenous immunoglobulin (IVIg) used as induction with maintenance immunosuppression provides excellent results. Akalin et al studied the effect of rATG and IVIg on the outcome of 8 CDC T cell negative, CDC B cell positive crossmatch recipients who were also T or B cell flow cytometry positive. rATG dose was 1.5 mg/kg for 5 days accompanied by IVIg 100 mg/kg for 3 days and maintenance immunosuppression with cyclosporine, mycophenolate mofetil or sirolimus and prednisone taper. They report only one antibody mediated rejection and no cellular rejection with 14 months follow-up. One graft loss occurred from polyoma virus nephropathy and renal function was excellent with creatinine less than 1.1 mg/dl in the 5 patients without rejection and 2.3 mg/dl in the patient who suffered antibody mediated rejection. An extension of this trial and secondary analysis of the donor specific antibodies (DSA) after transplant suggested that the combination of rATG and IVIg downregulated preformed DSA (2 with class I and 4 with class II) but did not have a protective effect against de novo DSA. They note that 3 of 5 recipients with class I DSA developed early acute antibody mediated rejection indicating inadequate immunoprotection of the induction regimen. They increased the dose of the IVIg to 300–500 mg/kg with class I DSA and subsequently to 2000 mg/kg for all patients. Using this higher dose of IVIg, same dose of rATG and maintenance immunosuppression with tacrolimus, mycophenolate mofetil and corticosteroids, they treated 12 additional patients but found antibody mediated rejection in 4 of those recipients. On retrospective analysis of the DSA, they discovered that these 4 patients had strong class I DSA (characterized by baseline Luminex beads analysis of ≥ 6000 MFI). Therefore, in 23 additional patients they added peri-transplant plasmapheresis to reduce the incidence of antibody mediated rejection (4–8 sessions pre-transplant in living donor recipients and 3 sessions every other day post-transplant in deceased donor recipients). None of the patients with weak (baseline of 1500–3999) or moderate (4000–5999) DSA analysis had acute rejection of any form—they received the higher dose of IVIg but none were treated with plasmapheresis. In the strong DSA group, none of the 4 living donor and 1 of 10 of the deceased donor recipients suffered antibody mediated rejection. Median creatinine was 1.1–1.2 in all groups. No graft losses were reported in the weak/moderate DSA groups with median follow-up of 16 months. Only 1 graft loss was reported in the strong DSA group treated with IVIg/plasmapheresis after median 12 months. Mai et al used rATG 4.5–6 mg/kg, IVIg 1500 mg and maintenance therapy with tacrolimus, mycophenolate mofetil, and corticosteroids in 20 recipients defined as high immunological risk with CDC-AHG negative, flow cytometry positive crossmatch (retrospective flow bead analysis demonstrating DSA in 18). They compared outcomes to 2 control groups: low immunological risk recipients and high immunological risk patients with CDC and flow cytometry negative crossmatch, each treated with rATG only induction and the same maintenance regimen. Rejection occurred in 50% of the flow cytometry positive group (30% antibody mediated rejection), 25% of the flow cytometry crossmatch negative high immunological group (6% antibody mediated rejection) and 12% of the low immunological risk group (2% antibody mediated rejection). Graft and patient survival along with renal function (as determined by creatinine or measured GFR) was similar between groups at 2 years. Thielke et al report a desensitization protocol in 57 kidney recipients that had positive flow cytometry crossmatch using plasmapheresis and low...
dose IVIg +/- rituximab allowing transplantation in 51 attaining a negative flow cytometry crossmatch with living donor kidneys. Of the 51, 14 were either T or B cell CDC-AHG crossmatch positive, the others negative. Induction included rATG for a total dose of 6 mg/kg along with every other day plasmapheresis and low dose IVIg for one week. Each patient received maintenance immunosuppression with tacrolimus, mycophenolate mofetil and corticosteroids (the steroids were tapered off in 12 patients within the first 5 days). One year incidence of rejection was 43% (about half of these antibody mediated rejections). One and 2 year graft survival was 93 and 81% respectively. There was no difference in incidence of rejection or one year MDRD eGFR between those with initial flow cytometry T cell channel shifts greater than 70 compared to those less than 70. rATG appears to play a valuable role in reducing rejection risk in those with detectable low level DSA.

**Rejection: rATG Versus Equine Anti-Thymocyte Globulin**

The effectiveness of rATG to treat rejection was established in a trial comparing rATG to equine ATG (ATGAM). This multicenter, randomized, double-blind study of 163 kidney transplant recipients found that rATG reversed rejection in a greater percentage of patients (88% versus 76%, P = 0.027) and found less recurrent rejection (17% versus 36% P = 0.011) than equine ATG, respectively. This trial was the basis for rATG approval by the FDA in the United States for treatment of rejection in kidney transplantation. Antibody mediated rejection occurs more frequently in those kidney transplant recipients of high immunological risk. The basis of treatment of this form of rejection is: inhibition of the T-cell response, removal of circulating anti-donor antibody, inactivate residual antibody, and remove or inhibit B-cells. rATG possesses some of these characteristics and additional studies have looked at rATG in treating antibody mediated rejection, a common complication in those patients with high immunological risk. The basis of treatment of this form of rejection is: inhibition of the T-cell response, removal of circulating anti-donor antibody, inactivate residual antibody, and remove or inhibit B-cells. rATG was not used in either group to treat the antibody mediated rejection.

**Dose and Administration**

The recommended dose for rATG is 1.5 mg/kg intravenously daily for 7–14 days for the treatment of acute cellular rejection. Infection and cancer risks appear to be dose dependent so alternative dosing schedules have been explored. In induction trials, Klem et al describe results of using a total rATG dose of 4.5 mg/kg versus 6 mg/kg in 83 kidney transplant high immunological risk patients. The immunological risk was defined as those with PRA 20% or greater, repeat transplant, and African-American race. First dose of rATG was given intra-operatively. Maintenance immunosuppression
primarily consisted of tacrolimus/mycophenolate mofetil/corticosteroids in those receiving 4.5 mg/kg and mainly tacrolimus/sirolimus/corticosteroids in those receiving 6 mg/kg. Choice of dose of rATG was arbitrary, but the lower dose was commonly used in those with better graft function by post-operative day 2. The incidence of rejection or infection complications with one year of follow-up was similar between groups and not statistically different. Limitations of this study included its retrospective nature, exclusion of those recipients who developed delayed graft function, and the influence of post-operative kidney function on choice of rATG dose.

Gurk-Turner et al retrospectively reviewed the use of rATG induction in 96 high immunological risk kidney transplant recipients (repeat transplant or PRA ≥ 40%).75 Total dose of rATG was initially targeted at 10.5 mg/kg and higher, but smaller doses were administered because of adverse drug effects or by investigator choice. Those that received 7.5 mg/kg rATG or less were compared to those that received >7.5 mg/kg. First dose of rATG was given intra-operatively and maintenance immunosuppression consisted of tacrolimus/mycophenolate mofetil/ corticosteroids. All patients had at least one year follow-up. There was no statistical difference in graft survival, biopsy proven rejection or 1 year serum creatinine between the groups. Caution should be used in interpreting the efficacy of lower dose rATG in these high risk groups because the data was collected retrospectively and the total dose of rATG was electively chosen in some patients.

Agha et al demonstrated the efficacy of a 3 day course of rATG (3 mg/kg intra-operatively and 1.5 mg/kg on 2 subsequent days for total of 6 mg/kg) when compared to historical controls with longer therapy of 7 days.76 Hardinger et al showed excellent outcomes using a 6 mg/kg total dose of rATG.77 Wong et al reported a total rATG dose of only 3 mg/kg was found to have similar rejection rates (0% reported in a total of 16 patients treated) to 4.5 mg/kg dose and equal renal function at 2 years.78 The patients in these studies were not considered high immunological risk. But Peddi et al described high immunological risk kidney and kidney-pancreas recipients receiving rATG based on CD3 counts, with each patient getting an average of 4.2 mg/kg (or three 1.5 mg/kg doses) with good safety profile, low rates of rejection, and cost savings because of less rATG used.79 Overall, a total induction dose of 6–7.5 mg/kg is recommended to safely prevent rejection in those considered high immunological risk until additional trials confirm efficacy of lower doses.13

Timing and manner of administration of rATG has been explored. In use of rATG for induction, the first dose should be administered intra-operatively given findings of decreased delayed graft function.15 High-flow veins for infusion are recommended by the manufacturer to decrease the risk of phlebitis. Reports have demonstrated safe dispensing of rATG by peripheral vein with or without co-administration of heparin and/or corticosteroids.80,81 rATG given by peripheral vein was tolerated as well as those patients receiving basiliximab.80

Safety

Ten year safety data is available on the use of rATG. Hardinger et al followed 48 patients who had received rATG as induction therapy (1.5 mg/kg) for 7 days and maintenance with cyclosporine, azathioprine or mycophenolate mofetil, and corticosteroids.32 The incidence of CMV disease was 13% with no polyoma virus nephropathy. The lymphocyte counts at 10 years were 1.5 ± 0.7 cells/mm³. Noncutaneous malignancy occurred in 6% and there were no reported cases of post-transplant lymphoproliferative disease (PTLD). The maintenance immunosuppression was different than that commonly used with high immunological risk patients today so this safety record may not reflect current immunosuppression. Although the follow-up is impressive, the numbers were small.

Many have analyzed the safety of rATG with respect to malignancy, particularly post-transplant lymphoproliferative disease -PTLD. Short-term studies have not demonstrated an increased risk of malignancy (PTLD or solid tumors) in comparisons of rATG to basiliximab or rATG to daclizumab, but the follow-up was only 1 year.34,42 Three registry studies have failed to show an increased risk of PTLD with the use of rATG when compared to no induction.37,82,83 Please note that the follow-up of patients receiving rATG was shorter than the comparator arm in 2 studies (13 versus 25 months in the Caillard et al report and 368 versus 1433–2055 days in the Dharnidharka and Stevens paper) and only 727 days in the Cherikh paper (rATG was not separately analyzed from other polyclonal
antibody induction in this report). In contrast, Bustami et al described outcomes of nearly 42,000 first deceased donor kidney transplant recipients followed for approximately 4 years.84 They showed a higher risk of developing PTLD in the rATG patients as well as those receiving murimonab-CD3, daclizumab, basiliximab; without significant differences between the different induction agents. There was no increased risk using induction versus no induction regarding solid tumors. Kirk et al also showed increased risk of PTLD in those patients receiving rATG induction and followed for 730 days.85 The unadjusted incidence of PTLD was significantly higher for the induction group versus the non-induction group, (95% CL 1.188–2.235, P = 0.025) for rATG versus no induction and no increased RR for the other induction agents.

Early reports suggest that rATG induction was associated with a higher risk of CMV. Mourad et al describe an incidence of CMV of 32.5% in the rATG induction group versus 19.0% in the non-induction group, P = 0.009.86 Charpentier et al report a rate of CMV infection of 24.2% and 28.3% in the rATG induction groups using tacrolimus and cyclosporine respectively versus 15.7% in the non-induction group, P = 0.012.87

In the former paper, only 13.9% of the patients received viral prophylactic therapy while in the latter study the use of anti-viral therapy is not specified.

Summary
rATG provides clinical benefit in treating and preventing rejection in high immunological risk kidney transplant recipients. Exploration of dosing options continues in an effort to improve safety and cost-effectiveness.

Disclosure
This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

References

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