Induction Immunosuppression in High-risk Kidney Transplant Recipients

Jesmar Buttigieg,1,2 Julie M. Bridson,2 Ajay Sharma,2,3 Ahmed Halawa2,4

Abstract

Kidney transplant remains the best type of renal replacement therapy in most patients with end-stage kidney disease, even in those with high immunologic risk. Immunosuppression in these patients is regarded as more complex, owing to the higher risk of both acute and chronic rejection. The advent of induction immunosuppression has resulted in a lower incidence of acute rejection and consequently improved short-term patient and allograft outcomes. Indeed, the use of these agents, especially in high-risk recipients, has become standard of care at most transplant centers. Transplant physicians are constantly faced with the challenge of estimating the recipients’ immunologic risk and tailoring their immunosuppression accordingly. This review article aims to provide an up-to-date evaluation of the various studies available, which investigated the use of induction agents in kidney transplant, specifically in high-risk recipients. It evaluates the use of the most frequently used polyclonal antibody (rabbit antilymphocyte globulin) versus the less commonly used monoclonal antibody alemtuzumab, superseded agents such as muromonab-CD3, and potentially emerging agents such as rituximab, bortezomib, and eculizumab. With this systematic review, we hope to inform the scientific community and facilitate this controversial decision through the implementation of robust scientific evidence.

Key words: Antilymphocyte serum, Graft survival, HLA antigens, Monoclonal antibodies, Rejection

Introduction

The human immune system has evolved over millions of years to ensure adequate protection against various microbial pathogens present in our environment. The antigen-host interaction is initiated via a process called allore cognition, whereby any foreign protein is exhibited on an HLA antigen molecule and becomes recognized by the host immune system.1 It is thought that this process starts immediately once the arterial clamps are snapped open and the transplanted organ is perfused for the first time by the host circulation. T lymphocytes orchestrate the subsequent effector response, leading to rejection of the transplanted tissue. With the exception of transplant between monozygotic twins, immunosuppression remains an integral part of modern transplant medicine. In HLA- and ABO-compatible kidney transplant, immunosuppression falls under 3 main categories: induction, maintenance, and rescue therapy. Induction immunosuppression is a prophylactic treatment using biologic agents that deplete or modulate the activation of lymphocytes in the peritransplant and immediate posttransplant periods. The principal aim is to alter this highly immunogenic instance and perhaps facilitate late introduction of calcineurin inhibitors, especially when delayed graft function (DGF) is expected. In addition, oral agents might not be sufficiently effective in the first few days because of their inherent pharmacokinetics properties. Various randomized controlled studies and meta-analyses have consistently showed that induction therapy and maintenance immunosuppression are associated with less rejection episodes compared to maintenance therapy alone.2-4 The most favorable induction strategy depends on the estimated immunologic risk and remains a rather debatable topic among different transplant centers.5 According to the Organ Procurement and Transplantation Network and

From the 1Renal Division, Department of Medicine, Mater Dei Hospital, Malta; the 2Faculty of Health and Science, Institute of Learning and Teaching, University of Liverpool, United Kingdom; the 3Royal Liverpool University Hospital, Liverpool, United Kingdom; and the 4Sheffield Teaching Hospitals, Sheffield, United Kingdom

Acknowledgements: The authors declare that they have no sources of funding for this study, and they have no conflicts of interest to declare.

Corresponding author: Jesmar Buttigieg, Renal Unit, Mater Dei Hospital, Malta Phone: +356 2545 6080 E-mail: jesmar.buttigieg@gov.mt

Experimental and Clinical Transplantation (2016) 4: 367-376

DOI: 10.6002/ect.2015.0328
Scientific Registry of Transplant Recipients annual data, there was an overall reduction in the use of interleukin 2 receptor antagonists (IL-2ra) and a corresponding rise in use of antilymphocyte agents (ALAs), reaching 56.2% of all recipients in 2012.6

**Aims and Methods**

Our aim of this critical reflection was to systematically investigate this controversial subject in high-risk kidney transplant recipients. This critical review was limited to studies that investigated the effects of induction agent on the short- and long-term outcomes of transplant recipients classified as high immunologic risk. Literature searches were performed via MEDLINE, EMBASE, PubMed, Google Scholar, and Scopus, using the following medical subject headings: induction, prophylactic, therapy/immunosuppression, antilymphocyte, biologic or biologics, alemtuzumab, IL-2ra (basiliximab/ daclizumab), rituximab, bortezomib, eculizumab, high immunologic risk, and kidney or renal transplant. All relevant registry analyses, randomized controlled trials, and retrospective cohort studies describing the use of induction agents in high-risk adult kidney transplant patients were included. Case reports or series that included ≤ 3 patients were excluded.

**Induction immunosuppressive agents**

Induction immunosuppression falls under 2 main categories: (1) IL-2ra, also known as nondepleting agents, which include basiliximab and daclizumab; and (2) ALAs, also known as depleting agents, which are further subdivided into the following: monoclonal agents such as muromonab-CD3, alemtuzumab, and rituximab; and polyclonal agents, including rabbit antithymocyte globulin (rATG) and equine antithymocyte globulin (ATGAM; Pfizer).

**Muromonab-CD3**

Muromonab-CD3 (Orthoclone [OKT3]; Centocor Ortho Biotech, L.P) is a murine monoclonal antibody directed against the CD3 receptor on T lymphocytes (Figure 1). Antibody-receptor interactions induce widespread T-lymphocyte dysfunction.7,8 Muromonab-CD3 has been associated with severe cytokine release syndrome, pulmonary edema, and gastrointestinal and neurologic disturbances.9 There is paucity of quality data on its clinical use, safety profile, and effectiveness. Its use in kidney transplant has been largely superseded by safer induction agents, and it was recently withdrawn from the US market.

**Antithymocyte globulin**

Antithymocyte globulin (ATG) is produced by active immunization of rabbits (rATG) or horses (ATGAM) with human lymphoid tissue. The mechanism of action is not completely understood, but it ultimately leads to complement lysis of various immunocompetent cell lineages. Recovery of the immune system may take months to years and may not recover entirely, especially with increasing age.10 The main adverse effects include cytokine release syndrome, pyrexia, hypotension, thrombocytopenia, leukopenia, and serum sickness.9

**Meta-analyses investigating the use of depleting antilymphocyte agents versus no induction**

In 1997, a meta-analysis conducted by Szczepch and associates3 analyzed 7 randomized controlled trials involving 794 patients receiving either muromonab-CD3 or polyclonal ALA versus no treatment or placebo.11-17 This demonstrated an overall reduction in deceased-donor graft failure with ALA and a 6% increase in survival in the first 2 years.3 A second meta analyses by Szczepch and associates in 1984 investigated individual patient-level data involving
5 of the previously studied randomized controlled trials.\textsuperscript{12,14-17} Among the broad spectrum of high-risk patients studied (n = 628), reduction in allograft failure was greater in patients with panel reactive antibody (PRA) ≥ 20\% (ratio of adjusted rate of 0.12, 95\% confidence interval, 0.03-0.44; \( P = .002 \)) compared with patients who were not sensitized at 2 years.\textsuperscript{10} Comparable data were obtained at 5 years.

**Retrospective single-center studies investigating use of rabbit antithymocyte globulin**

Mai and associates compared the outcomes of patients who received first grafts from donations after cardiac death (n = 40) versus donations after brain death (n = 142) between 2005 and 2009.\textsuperscript{18} All patients received induction with rATG (cumulative dose of 6 mg/kg), and steroids were discontinued by day 5. Patients were maintained on tacrolimus and mycophenolate mofetil (MMF). Both groups had no significant difference in the incidence of biopsy-proven acute rejection (BPAR), serum creatinine level, and graft survival at 2 years. This may suggest that rATG induction, even with rapid steroid taper, may confer similar results in kidney donations after cardiac death versus kidney donations after brain death despite higher immunologic risk. In a study conducted in Korea between 2002 and 2009, Kim and associates compared rATG (n = 152) with basiliximab (n = 362) induction.\textsuperscript{19} Basiliximab was given at standard dose and rATG was given at 1.5 mg/kg for 5 to 7 days. All patients were maintained on tacrolimus or cyclosporine, MMF, and steroids. As with many retrospective studies, the baseline characteristics indicated considerable center bias. Indeed, patients with higher PRA, who had been retransplanted, and who had received deceased-donor kidneys were significantly more likely to receive rATG induction. Although these patients had a higher immunologic risk, there was no significant difference in the rate of acute rejection and graft or patient survival at 1 year. However, there was a significant increase in *cytomegalovirus* infections and DGF rates.

**Retrospective analyses using registry data**

Patlolla and associates analyzed the Scientific Registry of Transplant Recipients database and compared induction using IL-2ra versus use of ALA (equine ATG, rATG, and muromonab-CD3) and no induction in 448 948 patients receiving their first renal transplant between 1998 and 2003.\textsuperscript{20} Maintenance immunosuppression patients who received ALA had a higher immunologic risk, defined as black ethnicity, > 3 HLA antigen mismatches, > 1 HLA-DR mismatch, higher PRA, longer cold ischemia time, more DGF, and older donor age. The use of ALA was associated with a significant 10\% reduction in the incidence of acute rejections compared with IL-2ra at 1 year. Interestingly, there was a trend toward increased graft failure at 6, 12, and 36 months after transplant with ALA. The higher immunologic risk of the ALA group has to be factored in when interpreting this outcome. Jindal and associates used the US Renal Data System database to study 37 470 kidney transplants from 2000 to 2005.\textsuperscript{21} The study compared graft outcomes in patients receiving either rATG or IL-2ra, particularly between African American and white patients. Patients who received rATG were more likely to have been older, with elevated body mass index and of African American descent, received grafts from donors after cardiac death, showed PRA > 20\%, and experienced DGF. Despite favorable immunologic risk in the IL-2ra group, patient and graft survival were comparable between African American and white recipients. Finally, Willoughby and associates used the Organ Procurement and Transplantation Network database to investigate 19 137 recipients who received either rATG or basiliximab between 2001 and 2005.\textsuperscript{22} Patients who received no induction were used as the reference group, and all patients were maintained on tacrolimus and MMF with or without steroids. The composite triple endpoint was defined as allograft rejection, graft failure, or patient death at 6 months after transplant. Patients who received rATG together with steroids were more likely to be of black ethnicity, obese, presensitized, recipients of an HLA-DR mismatched graft from older donors, and with higher incidences of cardiovascular comorbidities and DGF. Although patients who received rATG had a higher immunologic risk, the risk of the triple endpoint was significantly lower in the rATG group than in the basiliximab group regardless of steroid use (adjusted odds ratio of 0.78; 95\% confidence interval, 0.69-0.87 with steroids and adjusted odds ratio of 0.66; 95\% confidence interval, 0.44-1.00 without steroids). A 2.7\% and 4.7\% absolute reduction in the incidence of triple endpoint was shown in the rATG versus basiliximab group in those patients who received steroids and those who did not. Although registry analyses provide “real life”
long-term patient data and are useful benchmarks for future studies, they should always be interpreted with caution; recognizing their limitations is paramount before drawing conclusions. Nonetheless, these published analyses suggested that rATG is associated with less acute rejection and better outcomes than IL-2ra in high-risk transplant patients.

Randomized controlled trials investigating the use of antithymocyte globulin induction in high-risk kidney transplant patients

Thibaudin and associates conducted the first randomized, prospective, single-center study comparing rATG (n = 42) with no ATG (n = 42) in addition to standard therapy consisting of cyclosporine, azathioprine, and steroids in presensitized kidney transplant recipients between 1991 and 1995. The study included patients who received first or second transplants, patients who received deceased- or living-donor transplants, and patients with current or historical positive B-cell crossmatch. Panel reactive antibody was calculated using the lymphocytotoxic method, and pre-sensitized was defined as patients with PRA > 5%. Rabbit antithymocyte globulin lowered the incidence of BPAR from 64% to 38% (P = .02) and was beneficial in all presensitized patients. There was a borderline significant improvement in graft survival at 1 year. The second randomized controlled trial was conducted by Brennan and associates. This was a prospective, international multicenter, open-label, industry-sponsored randomized controlled trial that compared short courses of ATG (n = 141) with standard basiliximab dose (n = 137) in patients at high risk of acute rejection or DGF. At 12 months, the incidence of BPAR was significantly lower in the ATG group than in the basiliximab group (15.6% vs 25.5%; P = .02) as was the severity of acute rejection requiring the use of rescue ALA (1.4% vs 8%; P = .005). In contrast, the incidences of graft loss, DGF, patient death, major adverse effects, and malignancy were similar. Patients treated with ATG had a higher incidence of overall infection episodes (85.8% vs 75.2%; P = .03). Interestingly, cytomegalovirus infections were significantly higher in the IL-2ra group (7.8% vs 17.5%; P = .02). Brennan and associates continued follow-up of the US patients for 5 years. Composite endpoints were BPAR, DGF, graft loss, and patient death. The lower incidence of BPAR (15% vs 27%; P = .03) and lower incidence of composite endpoint (37% vs 51%; P = .04) in the ATG group was sustained even at 5 years. In 2009, Noel and associates conducted another prospective, multicenter, investigator-sponsored randomized controlled trial, but this one was in Europe. This study provided a head-to-head comparison of the efficacy and safety of rATG (n = 113) versus daclizumab (n = 114) among high-risk kidney transplant patients. High immunologic risk was defined as current PRA of > 30%, peak PRA > 50%, loss of a first kidney allograft attributed to rejection within 2 years, and 2 or 3 previous allografts. Patients treated with rATG had a lower incidence of both BPAR (15.0% vs 27.2%; P = .016) and steroid-resistant rejection (2.7% vs 14.9%; P = .002) at 1 year. The overall graft and patient survival rates were similar in the 2 arms, although patients who were free of rejection episode had higher graft survival compared with those with rejection (87.2% vs 75.0%; P = .037). There was less incidence of DGF in the rATG group than in the daclizumab group (31.5% vs 44.6%; P = .044). These advantages were unfortunately hindered by a significantly higher mean number of bacterial infections per patient (2.5 ± 1.8 vs 1.8 ± 1.2; P = .014) and a trend toward higher incidence of cytomegalovirus viremia requiring treatment (18.6% vs 10.5%; P = .093) in the rATG group compared with the daclizumab group. Helleman and associates followed the same cohort of patients for 5 years. Again, treatment with rATG was associated with lower incidence of BPAR compared with daclizumab (14.2% vs 26.0%; P = .035). Overall graft and patient survival rates remained similar in the 2 groups even at 5 years, although overall graft survival was significantly higher in patients without BPAR (81.0% vs 54.8%; P < .001). Table 1 summarizes the above-mentioned randomized controlled trials.

In conclusion, Noel and associates enrolled a higher number of retransplant patients (70% vs 10%) and patients with higher PRA levels (peak 72% vs 14%) compared with that shown in the study by Brennan and associates. Target ATG dose was also slightly higher (8.75 mg vs 7.5 mg/kg), used daclizumab rather than basiliximab, and maintained patients on tacrolimus (more common in modern regimens) rather than cyclosporine. However, the overall outcome was outstandingly similar, with a lower BPAR at 1 year and with no significant differences in the overall allograft or patient survival between the 2 arms.
Comparison between the 2 major antithymocyte globulins

Brennan and associates conducted a randomized, double blind, single-center comparison of thymoglobulin (n = 48) at 1.5 mg/kg versus equine ATG (n = 24) at 15 mg/kg. All patients received immunosuppression with cyclosporine, MMF or azathioprine, and steroids. The thymoglobulin group, when compared with the group that received equine ATG, had less incidence of acute rejections (4% vs 25%; \(P = .014\)), were more likely to be event free (patient survival, graft loss, or rejection; 94% vs 63%; \(P = .001\)), and had less adverse effects (\(P = .013\)) at 1 year. At 5 years, Hardinger and associates established more significant results. Patient who received thymoglobulin were more likely to remain event free (73% vs 33%; \(P \leq .001\)) and without acute rejection (92% vs 66%; \(P = .007\)) compared with equine ATG. The difference in the event-free survival was sustained even at 10 years. The difference in graft survival was however no longer statistically significant at 10 years. Kim and associates conducted a retrospective, single-center study in Korea, comparing patients who received thymoglobulin (n = 152) versus equine ATG (n = 84) between 1997 and 2010. All patients received tacrolimus or cyclosporine, MMF, and steroids. Patients receiving thymoglobulin were significantly older, had higher body mass index, had longer duration on dialysis, and had a higher number of retransplants. Thymoglobulin was significantly associated with higher incidence of DGF when compared with equine ATG (7.9% vs 0%; \(P = .005\)). Death-censored graft survival at 5 years was significantly higher in the thymoglobulin group than in the equine ATG group (96.8% vs 88.7%; \(P = .027\)), but creatinine levels and number of acute rejection episodes were similar. As with all retrospective studies, a degree of variability in the baseline characteristics is inevitable, and one should interpret these findings with a certain degree of caution.

Studies investigating the optimal antithymocyte globulin dose

Bacterial and viral opportunistic infections were lower when the total dose of ATG did not exceed 7 mg/kg. Gurk-Turner and associates conducted a retrospective cohort study looking specifically at the optimal ATG dose in high-risk kidney transplant recipients in the United States between 2000 and 2005. Patients were considered high risk if they had required retransplants or had a PRA > 40%. All patients received tacrolimus, MMF, and steroids. The absolute CD3 lymphocyte, platelet, and total white blood cell counts were closely monitored. At 18 months, there was no significant difference in the overall graft survival, and at 12 months there was no significant difference in the incidence of BPAR or serum creatinine levels between patients who received higher dose ATG (≥ 7.5 mg/kg; n = 63) and those who received a lower dose (< 7.5 mg/kg; n = 33).

Alemtuzumab

Alemtuzumab is a recombinant, humanized, monoclonal antibody, which targets the CD52 cell surface antigen present on T and B lymphocytes, natural
killer cells, some monocytes, and granulocytes (Figure 1). These cells will subsequently undergo a sustained complement-mediated lysis. The main adverse effects include mild cytokine release syndrome, pancytopenia, autoimmune thrombocytopenia, and thyroid disease.9

Retrospective studies investigating the use of alemtuzumab versus antithymocyte globulin
Schadde and associates investigated induction with alemtuzumab (n = 61) versus IL-2ra (n = 43) in low-risk recipients and alemtuzumab (n = 20) versus ATG (n = 21) in high-risk recipients of kidneys from donors after cardiac death.34 High-risk was defined as PRA ≥ 20%, retransplant, and African American background. All patients received triple maintenance therapy with calcineurin inhibitors, MMF, and corticosteroids. There was no significant difference in the rejection rate or glomerular filtration rate between the 2 induction modalities, but there was a trend of increased graft and patient death (P = .055) in patients who received alemtuzumab compared with ATG in the high-risk group. Noureldeen and associates conducted a single-center retrospective study to investigate alemtuzumab (single 30-mg dose; n = 68) versus rATG (total dose of 6 mg/kg; n = 40) between 2009 and 2011.35 Maintenance immunosuppression consisted of tacrolimus, MMF, and corticosteroids, which were discontinued in all except in sensitized recipients. Acute rejection episodes were similar in both groups. However, the alemtuzumab group had significantly higher incidence of antibody-mediated rejection than the rATG group (15% vs 2.5%; P = .008) at 1 year. This difference can probably be attributed to a significantly higher use of maintenance steroids in the rATG group, giving a favorable outcome.

Randomized controlled trials investigating the use of alemtuzumab versus antithymocyte globulin in high-risk renal transplants patients
This area of transplant immunology is characterized by small, underpowered studies with relatively short follow-up. Thomas and associates conducted a prospective, open-label randomized controlled trial that investigated the use of alemtuzumab induction with tacrolimus monotherapy versus rATG induction with standard triple therapy in high-risk kidney transplant recipients, defined as patients who currently have or have a history of PRA > 20% or retransplant.36 In an interval report published in 2007, the incidence of BPAR, infections, and cumulative patient and graft survival were similar at 1 year. Lu and associates conducted a similar study in the Chinese population, including 23 high-risk patients defined as PRA > 20%.37 These patients were randomized to either alemtuzumab or rATG, with both groups receiving standard maintenance immunosuppression composed of tacrolimus, MMF, and corticosteroids. Similar creatinine levels, graft and patient survival rates, and freedom from rejection episodes were reported at the 2-year follow-up. Although both studies were underpowered to draw any firm conclusions, the results obtained are encouraging and suggest that alemtuzumab induction may be a safe option in high-risk patients. In another single-center randomized controlled trial conducted by Farney and associates, a significantly higher rate of freedom from rejection episodes was reported in the alemtuzumab arm compared with the rATG arm.38 These results should be interpreted with the understanding that the study population was a combination of kidney alone, kidney and pancreas, and pancreas transplant recipients. Immunologic risk was different, with most patients belonging to the low immunologic risk group. Finally, maintenance immunosuppression also differed depending on the level of immunologic risk, with some patients having early steroid withdrawal and others having rapid withdrawal. These randomized controlled trials were followed by a study by Hanaway and associates. This was the largest, open-label, multicenter randomized controlled trial to date.39 Patients received either alemtuzumab or conventional induction therapy, which involved basiliximab in low-risk (n = 335) and rATG (n = 139) in high-risk patients. High risk was defined as patients with current or history of PRA ≥ 20%, retransplant patients, or black patients. In the high-risk group, 70 patients received alemtuzumab and 69 received rATG. Maintenance immunosuppression included tacrolimus, MMF, and corticosteroids (discontinued on day 5). Among the high-risk patients, there was no significant difference in BPAR rate at 6, 12, and 36 months between patients who received alemtuzumab and those who received rATG. The 3-year Kaplan-Meier actuarial patient survival curves in the high-risk group showed a trend toward better patient survival in the alemtuzumab group than in the rATG group (99% vs 91%; P = .07). There was no significant
difference in death-censored graft survival in the high-risk group when alemtuzumab was compared with rATG at 3 years. Among high-risk patients, there was a significantly higher rate of infection episodes in the rATG group than in the alemtuzumab group (81% vs 60%; \( P = .009 \)). Table 2 summarizes the above-mentioned RCTs.

Rituximab, Bortezomib, and Eculizumab

Rituximab is a chimeric monoclonal antibody directed against the CD20 transmembrane protein found on B lymphocytes (Figure 1).\(^\text{40}\) After binding, the B lymphocytes undergo lysis via both complement-dependent and complement-independent pathways.\(^\text{41}\) van den Hoogen and associates conducted a randomized controlled trial to assess the efficacy of rituximab as an induction agent in both low- and high-risk kidney transplant recipients.\(^\text{42}\) In this study, a PRA of > 6% or retransplant were considered as factors indicating high immunologic risk. Patients were randomized to either a single dose of 375 mg/m\(^2\) of rituximab (\( n = 138 \)) or placebo (\( n = 142 \)). Maintenance immunosuppression consisted of tacrolimus, MMF, and steroids. At 6 months, the overall incidence of BPAR was similar in the 2 arms. However, high-risk patients not treated with rituximab had a significantly higher incidence of acute rejection (38.2%) than rituximab-treated high-risk patients (17.9%), rituximab-treated low-risk patients (16.4%), and low-risk patients treated with placebo (15.7%) (\( P = .004 \)). Neutropenia was one of the main adverse events in patients receiving rituximab when compared with those who did not (24.3% vs 2.2%; \( P < .001 \)). To our knowledge, this is the only study to date that has investigated rituximab as an induction agent rather than a desensitizing agent. Results suggest that rituximab may have a role in the induction strategy of kidney transplant. Longer multicenter randomized controlled trials are essential to substantiate these results and to evaluate effectiveness against the standard induction therapies that are currently used.

We found no studies that investigated bortezomib and eculizumab as induction agents in ABO- and HLA antigen-compatible kidney transplant patients. These relatively novel agents are still sparingly used in the field of kidney transplant, and most data are available via case reports. Their use is reserved for desensitization in HLA antigen-incompatible transplant and resistant antibody-mediated rejection.\(^\text{43-46}\) Eculizumab is also effective for treatment of recurrent atypical hemolytic uremic syndrome.\(^\text{47}\)

**Discussion**

The use of ATG as an induction agent in high-risk transplant recipients definitely confers significantly

---

**Table 2. Summary of Randomized Controlled Trials Comparing the Use of Alemtuzumab and Antithymocyte Globulin as Induction Agents in Kidney Transplant Patients**

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-Up</th>
<th>Active Arm</th>
<th>Control Arm</th>
<th>Maintenance</th>
<th>Adverse Effects</th>
<th>Rejection Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomas et al(^\text{36})</td>
<td>12 mo</td>
<td>Alem (( n = 11 )): 30 mg single dose</td>
<td>rATG (( n = 10 )): 1.5 mg/kg until day 4</td>
<td>No statistical analyses</td>
<td>Freedom from AR: Alem 75.8% vs rATG 85.7% (not significant)</td>
<td></td>
</tr>
<tr>
<td>Lu et al(^\text{17})</td>
<td>24 mo</td>
<td>Alem (( n = 11 )): 15 mg on day 0 and day 1</td>
<td>rATG (( n = 11 )): 9 mg/kg bolus</td>
<td>Tac, MMF, steroids</td>
<td>No statistical analyses</td>
<td>Freedom from AR: Alem 81.8% vs rATG 72.7% (not significant)</td>
</tr>
<tr>
<td>Farney et al(^\text{38,4})</td>
<td>6 mo</td>
<td>Alem (( n = 48 )): 30 mg single dose</td>
<td>rATG (( n = 50 )): on alternate days, 1.5 mg/kg (3-7 doses)</td>
<td>Tac, MMF, steroids (early withdrawal/rapid taper)</td>
<td>Similar CMV, PVN, serious infection, PTLD rates</td>
<td>AR in kidney transplant alone: Alem 0% vs rATG 29%, ( P = .007 )</td>
</tr>
<tr>
<td>Hanaway et al(^\text{39,6})</td>
<td>36 mo</td>
<td>Alem (( n = 70 )): 30 mg single dose</td>
<td>rATG (( n = 69 )): 1.5 mg/kg (4 doses)</td>
<td>Tac, MMF, (steroids discontinued on day 5)</td>
<td>Infection episodes: Alem 60% vs rATG 81% (( P = .009 )); similar CMV and BK virus infections, UTI and PTLD</td>
<td>BPAR: Alem 18% vs rATG 15%, ( P = .63 )</td>
</tr>
</tbody>
</table>

**Abbreviations:** Alem, alemtuzumab; AR, acute rejection; BPAR, biopsy-proven acute rejection; CMV, cytomegalovirus; MMF, mycophenolate mofetil; PTLD, posttransplant lymphoproliferative disorder; PVN, polyomavirus nephropathy; rATG, rabbit antithymocyte globulin; Tac, tacrolimus; UTI, urinary tract infection

\(^\text{a}\)Study population was composed of 77 patients (79%) with kidney transplant alone, 17 patients (17%) with kidney and pancreas transplant, and 4 patients (4%) with pancreas transplant. Immunologic risk was different, with 70 patients belonging to the low immunologic risk group and 28 patients to the high immunologic risk group.

\(^\text{b}\)Only data and outcomes regarding the high immunologic risk patients are reported. The study was composed of 251 patients who received alemtuzumab and 250 patients who received conventional therapy, with 335 low-risk patients and 139 high-risk patients included in the primary analysis. BPAR rates were similar at 6, 12, and 36 mo.
less BPAR than IL-2ra. This is however achieved with
the caveat of higher infection episodes. The use of
ATG in this subgroup of renal transplant patients
failed to convey any significant advantages in terms
of graft or patient survival. These conclusions are
based on consistent moderate-quality evidence,
including 3 robust randomized controlled trials,
several registry analyses, and retrospective cohort
studies. One has to appreciate that the evidence is
less inclusive than with IL-2ra use in transplant.
Logically, it makes sense to stratify patients
according to their immunologic risk and to reserve
rATG for high-risk transplant patients, so that its
effectiveness against acute rejection is maximized
and the exposure to potential serious adverse effects
is minimized.
Improvement in overall graft and patient survival
rates is certainly considered one of the most
important measurable targets in kidney transplant;
however, one cannot simply use acute rejection as a
surrogate marker for graft or patient survival.
Conversely, numerous studies have established acute
rejection as an independent risk factor for graft
loss. In addition, patients who develop early
rejection were at a higher risk of developing chronic
allograft rejection. In 1 study, the cause for graft
failure was attributed to antibody-mediated rejection
in one-half of patients requiring an indication
biopsy. High-risk transplant recipients induced
with IL-2ra may ultimately require a higher
cumulative dose of steroids or still require ATG at a
later stage as rescue therapy. Prevention of acute
rejection episodes by use of appropriate induction
agents may ultimately result in a lower overall
immunosuppression burden and perhaps decreased
risk of infection and cardiovascular mortality.
Indeed, Schweer and associates established a higher
incidence of posttransplant type 2 diabetes mellitus
in patients requiring rescue treatment with steroid
pulses.
There have been few head-to-head comparisons
on the use of alemtuzumab versus ATG in high-risk
renal transplant patients. Data available suggest that
alemtuzumab does not confer any significant
additional advantages over ATG. To identify even
small differences in graft and/or patient outcomes,
randomized controlled trials need to be adequately
powered and patients followed for longer
periods. Long-term studies specifically investigating
development of de novo donor-specific antibodies
with different induction regimens are particularly
essential.

The economic aspect of such preparations is
another important issue worth considering.
Although this might not be of significant concern in
developed countries where health services are free at
the point of delivery, it certainly matters in countries
where the burden of immunosuppressive funding is
paid by the patients. Even though, the costs of these
preparations vary considerably between countries,
typically ATG is more expensive than Basiliximab,
Rituximab or Alemtuzumab (Campath; Genzyme).
Alemtuzumab is of recently being marketed under a
different brand name for multiple sclerosis
(Lemtrada; Genzyme), and the price has significantly
increased. Additionally, side effects, treatment failure
requiring alternative treatment and, of course,
hospital admission complicates any cost analysis.

Considering this cost variation and until novel
data become available, it is reasonable to use ATG for
induction in high-risk renal transplant patients,
provided that adequate antimicrobial prophylaxis is
instituted. In an editorial published in 2009,
Mandelbrot presented analogous suggestions:
administration of IL-2ra in low-risk transplant
patients and administration of rATG in high-risk
transplant patients. This recommendation is also in
line with the Kidney Disease Improving Global
Outcomes clinical practice guideline for
the care of kidney transplant recipients issued in
2009.

Another important consideration is the actual
definition of a “high-risk transplant” patient. Most
studies described here have used different definitions;
therefore, predicting pretransplant risk is another
source of controversy. Table 3 provides a tentative
definition of high-risk transplant by summarizing
various studies included in this review. The objective
of such an approach is to standardize therapy and
to assist nephrologists tailoring induction
therapy according to their patient’s baseline
characteristics.

Table 3. Definition of High-Risk Kidney Transplant According to Various
Studies Included in This Review

<table>
<thead>
<tr>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Current or historic panel reactive antibody ≥ 20%</td>
</tr>
<tr>
<td>2. Retransplant or multorgan transplant</td>
</tr>
<tr>
<td>3. More than 3 HLA antigen mismatches</td>
</tr>
<tr>
<td>4. Any HLA-DR antigen mismatch</td>
</tr>
<tr>
<td>5. Presence of donor-specific antibodies with negative Flow Cytometry Cross Match (FCXM)</td>
</tr>
<tr>
<td>6. African American recipient</td>
</tr>
<tr>
<td>7. Cold ischemia time &gt; 24 h or &gt;16 h + donor age &gt; 50 y</td>
</tr>
</tbody>
</table>
Conclusions

The use of ATG as induction agent in high-risk kidney transplant recipients is associated with less acute rejections than with IL-2ra, although possibly at the expense of a higher rate of infection. This conclusion is based on moderate-quality evidence delivered by robust randomized controlled trials that provided head-to-head comparisons with IL-2ra. Although these studies were not intended to investigate the optimal dose of ATG, the cumulative dose ranged from 7.5 to 10 mg administered perioperatively and during the immediate post-transplant period. The use of a single 30-mg dose of alemtuzumab appears to be equally effective to ATG at least in the short term. One promising advantage is the milder adverse effect profile; however, more robust data with longer follow-up are required. Unfortunately, both agents have failed to convey any significant advantages in terms of graft and patient survival rates. Considering the evidence to date, ATG should be the favored induction agent in high-risk renal transplant patients. Finally, multicenter collaboration and large registry data analyses are required to standardize the definition of “high immunologic risk,” which to date remains one source of significant bias and controversy in this field of kidney transplantation.

References


