Abstract

Induction therapy after kidney transplantation is intensive immunosuppression in the initial days after transplant when the immune system of the recipient has the first contact with donor antigens. Initial intensive immunosuppression may be required to prevent acute rejection and graft loss, and subsequent immuno-suppression may be decreased to minimize adverse events associated with immunosuppressive drugs. Induction agents include lymphocyte-depleting antibodies such as rabbit antithymocyte globulin, alemtuzumab, muromonab-CD3, rituximab, and bortezomib; lymphocyte-nondepleting antibodies such as interleukin 2 receptor antibodies; and other discontinued or investigational agents such as efalizumab and alefacept. Induction therapy may be adjusted for special situations such as living-donor kidney transplant, pediatric transplant, hepatitis C virus-seropositive recipients, recipients who require desensitization, patients who are at risk for developing delayed graft function, and old donors. The optimal immunosuppressive regimen may vary, and clinical practice guidelines are available.

Key words: End-stage renal disease, Antithymocyte globulin, Rituximab, Interleukin 2 receptor, Acute rejection, Delayed graft function

Introduction

Induction therapy is intensive immunosuppression in the initial days after transplant when the immune system of the recipient has the first contact with donor antigens. Induction therapy frequently is used to avoid early acute rejection that may predict graft loss.

Many randomized, controlled trials and meta-analyses show that induction therapy is better with antibodies and immunosuppressive drugs than drugs alone in reducing kidney allograft rejection and failure. However, the optimal prophylactic induction immunosuppressive therapy is controversial. There are many antibodies available for induction therapy that deplete lymphocytes or do not deplete lymphocytes.

The purpose of this article is to review the different indications for induction therapy, types of induction agents, and special considerations about induction therapy including transplant with living donors, children, recipients who have hepatitis C virus, desensitization, delayed graft function, and clinical practice guidelines.

Indications

Strategies for induction therapy include using either high doses of typical immunosuppressive agents or monoclonal or polyclonal antibodies. The purpose of induction therapy is to reduce the risk of acute rejection, decrease maintenance immunosuppressive doses, and improve outcomes in high-risk patients such as children, African Americans, recipients who have human leukocyte antigen (HLA) mismatches, and recipients who are sensitized to HLAs. Induction therapy may augment immunosuppression, facilitate delayed introduction of calcineurin inhibitors, induce tolerance, and minimize the need for immunosuppressive drugs.

Induction Agents: Depleting Antibodies

Depleting antibodies are polyclonal or monoclonal antibodies that deplete lymphocytes in transplant...
recipients by binding to antigens on lymphocytes such as the major histocompatibility complex antigens.\(^5\)

**Rabbit antithymocyte globulin**

Antithymocyte globulin (ATG) includes polyclonal antibodies that are generated in rabbits (rATG) (Thymoglobulin, Genzyme, Cambridge, MA, USA) or horses (equine ATG) (Atgam, Pfizer, New York, NY, USA) and used as immunosuppressive agents. These products are different than other rATGs (Fresenius, Bad Homburg, Germany) because the immunogens for rATG (Thymoglobulin) are human thymocytes and the immunogen for rATG (Fresenius) is a Jurkat T-cell leukemia cell line, and these rATG preparations differ in potency and efficacy. Equine ATG is a purified gamma globulin solution that is obtained by immunizing horses with human thymocytes.

The ATGs are antibodies commonly used as induction agents, but they are approved by the United States Food and Drug Administration (FDA) for corticosteroid-resistant rejection and acute cellular rejection (dose, 1.5 mg/kg for 7-14 d) based on the results of a multicenter, double-blind randomized trial.\(^6\) Induction regimens vary (range, 1-6 mg/kg/dose for 1-10 d; typical regimen, 1.5 mg/kg for 3-5 d).\(^7\) Common adverse events include cytokine release syndrome, leukopenia, and thrombocytopenia. The use of ATGs has been reviewed extensively.\(^8\)

A comparison was performed in 2 multicenter induction trials between rATG and basiliximab with either drug used in combination with cyclosporine, mycophenolate mofetil, and corticosteroids. In 1 trial of kidney transplant in low-risk patients, basiliximab with early initiation of cyclosporine was compared with rATG with delayed cyclosporine initiation, and both regimens had a similar incidence of acute rejection and similar patient and graft survival at 12 months after transplant.\(^9\) In the larger second trial with moderate-to high-risk deceased-donor recipients, the combined endpoint for the incidence of rejection, graft loss, and patient death was better for rATG (19.1\%) than basiliximab (31.6\%; \(P = .01\)).\(^10\) Most of the benefit of rATG in the combined endpoint was attributed to the decreased incidence of acute rejection with rATG (14.2\%) than basiliximab (25\%; \(P = .013\)).\(^11\)

**Alemtuzumab**

Alemtuzumab (Campath-1H, Genzyme, Cambridge, MA) is a humanized anti-CD52 panlymphocytic (both B and T cells) monoclonal antibody. A recombinant DNA-derived humanized monoclonal antibody that is directed against CD52 is currently approved by the FDA for treatment of B-cell chronic lymphocytic leukemia. However, it also has had off-label use for induction therapy and treatment of acute rejection.\(^12\) Infusion reactions may occur during intravenous administration (30 mg, 1 dose). The subcutaneous route also has been studied but is not approved by the FDA.\(^13\) The early use of alemtuzumab in kidney transplant recipients was associated with intense and prolonged lymphocyte depletion, increased antibody-mediated graft rejection, and increased frequency of serious infection.\(^14\)

Few small, randomized trials have been published about alemtuzumab after kidney transplant.\(^15\) The largest multicenter, randomized trial of alemtuzumab induction was stratified by low-risk (alemtuzumab compared with basiliximab; \(n=335\)) or high-risk patients (alemtuzumab compared with rATG; \(n=139\)). All patients received tacrolimus and mycophenolate mofetil, and steroids were withdrawn early. Expanded-criteria donors and non-heart-beating donors were excluded. Follow-up at 3 years showed that the frequency of biopsy-confirmed acute rejection was significantly lower in the alemtuzumab group (13\%) than basiliximab or rATG groups combined (20\%; \(P = .03\)). However, this benefit did not translate to improved graft survival or improved renal function. Acute rejection at 3 years was significantly less frequent in low-risk patients who had alemtuzumab (10\%) than basiliximab or rATG (22\%; \(P = .003\)). In high-risk patients, alemtuzumab and rATG had similar efficacy. In clinical practice, the lower frequency of acute rejection is considered against the risk of infection and cancer. The frequency of serious adverse events related to cancer was higher in the basiliximab or rATG therapy group, but the low-risk alemtuzumab group had persistent leukopenia and a higher frequency of serious infection.\(^16\)

**Muromonab-CD3**

Muromonab-CD3 (OKT3, Janssen Pharmaceutica NV, New Brunswick, NJ, USA) is a mouse antibody that depletes T cells by binding to the T-cell-receptor-
associated CD3 glycoprotein. Muromonab-CD3 has been used without having received approval in the United States by the FDA as an induction agent. Muromonab-CD3 has many adverse events including first-dose effect, pulmonary edema, nephropathy, infection, and malignancy. Preparations of ATG are better than muromonab-CD3 in tolerability and decreasing the incidence of acute rejection. Therefore, use of muromonab-CD3 was decreased and production was stopped in 2009.

Rituximab

Rituximab is a chimeric monoclonal antibody against CD20, an antigen that is expressed on most B cells. Rituximab was approved in 1997 for treatment of refractory B-cell lymphoma, and it has been used to treat autoimmune diseases. In kidney transplant, rituximab has been used for treatment of antibody-mediated rejection and desensitization in transplants incompatible in ABO antigens and/or HLA profile. Rituximab induction was evaluated in desensitization of 78 ABO and/or HLA incompatible transplant recipients who also received double-filtration plasmapheresis (3 to 4 sessions) before transplant. There was a significantly lower incidence of acute cellular rejection in patients who received rituximab (8.2%) than patients who did not receive rituximab (23.3%; \( P \leq .05 \)), but antibody-mediated rejection was similar in the 2 groups (rituximab, 6.8%; no rituximab, 8.3%; NS [not significant]). There was depletion of anti-HLA antibodies to class 1 (70%) and class 2 (83%) for > 2 years after rituximab induction. The 2 groups had similar incidence of cytomegalovirus infection (rituximab, 26%; no rituximab, 29%; NS) and leukopenia (rituximab, 23%; no rituximab, 14%; NS) and similar excellent 2-year frequency of survival of patients (rituximab, 100%; no rituximab, 98%; NS) and grafts (rituximab, 99%; no rituximab, 100%; NS).

Therefore, rituximab is a safe and effective induction antibody for the desensitization protocol in ABO- or HLA-incompatible transplants.

In a study of transplants that did not require desensitization, acute cellular rejection within 3 months after transplant was more frequent with induction with rituximab (5 of 6 patients [83%]) than daclizumab (1 of 7 patients [14%]; \( P = .01 \)). However, in a randomized, double blind multicenter study in patients who received induction with rituximab (n=68) or placebo (n=68) and maintenance with tacrolimus, mycophenolic acid, and steroids, treatment failure (defined as acute rejection, graft loss, or death) within 6 months after transplant was similar in patients who received rituximab (10 patients) or placebo (14 patients, not significant); the frequency of acute rejection, infection, and leukopenia was similar in the rituximab and placebo groups. Long-term study is needed to confirm the benefits of rituximab induction for nonsensitized patients.

Bortezomib

Allospecific antibody-secreting cells are long-lived plasma cells in bone marrow (CD138+CD20-). Therefore, the inhibitory effect of rituximab may be weak. Splenic and bone marrow plasma cells typically are resistant to common desensitization regimens, and alternative programs are needed. Bortezomib, a selective inhibitor of the 26S proteasome, is approved for treatment of multiple myeloma and is efficient in depleting nonmalignant plasma cells in experimental models. However, a study with a single cycle of bortezomib alone showed no or little effect of this antibody on decreasing the levels of donor-specific antibodies; therefore, bortezomib may be limited when used alone as desensitization therapy for acute antibody-mediated rejection. Further study of bortezomib is justified in prospective, randomized controlled studies because steroids and proteasome inhibitors such as bortezomib may act synergistically to target plasma cells, and a combination of these 2 drugs may be beneficial.

Induction Agents: Nondepleting Antibodies

Nondepleting antibodies do not deplete lymphocytes in transplant recipients but may provide immunosuppressive activity by other mechanisms. Full T-cell activation causes calcineurin-mediated stimulation of the transcription, translation, and secretion of interleukin 2 (IL-2), an important growth factor that induces T-cell proliferation. Therefore, administration of anti-IL-2 receptor (IL-2R) antibodies may interfere with IL-2 activity and prevent T-cell–mediated rejection. There are 2 IL-2R antibodies available: the chimeric monoclonal antibody basiliximab (Simulect, Novartis, Basel, Switzerland) and the humanized antibody daclizumab (Zenapax, Roche, Basel, Switzerland). Basiliximab and daclizumab bind to the \( \alpha \) chain of the IL-2R complex (CD25) that is...
expressed on activated T cells. As a result, T-cell activation and proliferation are prevented without cell lysis or depletion.

The IL-2R antibodies were introduced in 1997 and approved by the FDA for induction therapy. These antibodies have the best safety profile compared with other available induction antibodies and have no increased risk of infection or malignancy.27 The IL-2R antibodies have been evaluated in numerous placebo-controlled, randomized trials and are associated with less frequent acute rejection (28%) than placebo (42%).28 A meta-analysis showed that the risk of acute rejection is significantly less in patients who receive IL-2R antibody induction than placebo within 6 months (12 trials; relative risk, 0.66; 95% CI: 0.59-0.74) and 1 year after transplant (10 trials; relative risk, 0.67; 95% CI: 0.60-0.75).1 There was a similar incidence of cytomegalovirus infection and malignancy at 1 year between IL-2R antibodies and placebo.1

Basiliximab and daclizumab have similar efficacy and safety, but basiliximab has a more convenient schedule of administration (basiliximab, 2 doses within 4 days of transplant; daclizumab, 5 doses over 8 weeks).27 Therefore, basiliximab was more frequently used, and daclizumab was voluntarily withdrawn from clinical use by the manufacturer in October 2008, leaving basiliximab as the only IL-2R antibody currently available.

Basiliximab induction is safe and adequate for kidney transplant, including high-risk transplants. These high-risk transplants include deceased-donor kidney transplant in highly sensitized patients, simultaneous kidney and pancreas transplant, and split single pediatric donor kidney transplant.29-31 Typical triple therapy (tacrolimus, mycophenolic acid, and steroids) is used as maintenance immunosuppression. Evaluation of data from the United States Renal Data System from 2000 to 2005 showed that the frequency of patient survival and frequency of graft survival were similar in white and black patients who had induction with ATG or IL-2R antibodies.32

**Induction Agents: Discontinued and Investigational Agents**

**Efalizumab**

Efalizumab (Raptiva, Genentech, San Francisco, CA, USA) functions as an immunosuppressant by binding to the CD11a subunit of lymphocyte function-associated antigen 1 and inhibiting white blood cell migration. Efalizumab was indicated for the treatment of chronic moderate-to-severe plaque psoriasis.33 Clinical trials in kidney transplant recipients failed. The frequency of patient survival, graft survival, and acute rejection was similar between combination therapy with efalizumab (0.5 or 2 mg/kg, subcutaneous, once weekly for 12 wk), cyclosporine, mycophenolate mofetil, and steroids compared with half-dose cyclosporine, sirolimus, and prednisone. However, 3 of 38 patients (8%) who were treated with higher doses of efalizumab after transplant developed lymphoproliferative disease, and efalizumab was withdrawn from clinical use in April 2009. A study to replace calcineurin inhibitors with efalizumab soon after transplant in patients who had mildly impaired renal function was planned but terminated.34

**Alefacept**

Alefacept (Amevive, Astellas Pharmas, Deerfield, IL, USA) is an inhibitor of the costimulation of T cells by CD2 and lymphocyte function-associated antigen 3.35 It was approved by the FDA for treatment of moderate-to-severe chronic plaque psoriasis in adults (15 mg/wk, intramuscular, for 12 wk). The most common adverse event is lymphopenia, and dosage adjustments are made by monitoring CD4+ lymphocyte counts. No cumulative adverse events were observed in a study of multiple courses of alefacept; however, infections and malignancy may occur in patients treated with alefacept, and liver function should be monitored.36

Alefacept currently is being developed for use in conjunction with tacrolimus, mycophenolate mofetil, and steroids after kidney transplant. A multicenter, randomized, double-blinded, placebo-controlled, parallel-arm study in adult kidney transplant patients compared alefacept (n=105) to placebo (n=107).37 Study patients received alefacept (7.5 mg, intravenous, on days 0 and 3; 15 mg, subcutaneous, on day 7 and weekly; total, 12 wk). Follow-up at 6 months showed that the incidence of delayed graft function, renal function, biopsy-proven acute cellular rejection, patient survival, and graft survival were similar between patients who received alefacept or placebo.37 The overall incidence of infection was similar between patient groups, but alefacept was associated with a higher frequency of cytomegalovirus (alefacept, 14.3%; placebo, 7.5%) and
a lower incidence of BK virus infection (alefacept, 2.9%; placebo, 9.4%). Alefacept also was associated with a higher incidence of malignancy (alefacept, 6.7%; placebo, 0.9%) and lower levels of CD4+ and CD8+ memory T cells at 12 weeks after transplant. A study in 4 groups is ongoing with calcineurin reduction, mycophenolic mofetil replacement, alternative alefacept dose, and control. Further results of trials with alefacept are pending.37

**Special Situations**

**Living donors**

There is controversy about the effect of induction therapy in living-donor kidney transplant recipients. There is no economic benefit of basiliximab induction in adult living-related kidney transplant recipients and no differences in the incidence of acute rejection, renal function, or frequency of infectious complications between recipients of living-donor kidney transplant with or without induction.38 However, induction is important in living-unrelated kidney transplant. There is a higher frequency of acute rejection after 6 and 12 months, and a 3-fold greater risk of rejection, with living-unrelated kidney transplant without induction than deceased-donor kidney transplant with induction.39 Other studies of induction therapy in living-donor kidney transplant recipients showed that basiliximab significantly reduces the incidence of acute rejection episodes.40 Anti-IL-2R antibody therapy after living-donor kidney transplant is associated with lower graft failure at 1 year, lower hazard ratio for rejection by 13%, and lower risk of rejection by 13%.41 Living-donor kidney transplant recipients who receive induction therapy have better patient survival (98% to 100%) and graft survival (93% to 100%).42 Acceptable graft survival in ABO-incompatible living-donor kidney transplant may be achieved with plasmapheresis, splenectomy, and induction with ATG.43 In addition, after laparoscopic donor nephrectomy with longer warm ischemia times, basiliximab induction and a sirolimus and prednisolone regimen enabled the delayed use of cyclosporine and was associated with excellent 1-year graft survival.44

**Pediatrics**

Induction therapy is important in children to minimize the risks of steroids and calcineurin inhibitors and to achieve better growth and fewer adverse events. Basiliximab (10 mg for children who weigh < 35 kg) given at transplant and postoperative day 4 may cause saturation of IL-2R for 3 weeks.45 Basiliximab is safe within 1 to 2 months after kidney transplant in children who have low risk for *human herpesvirus* 6 or Epstein-Barr virus infection.46 Induction therapy with basiliximab for pediatric transplant recipients who are maintained on steroids, cyclosporine, and azathioprine may reduce acute rejection at 6 months and *cytomegalovirus* disease in *cytomegalovirus*-seropositive recipients, with better graft survival and function in long-term follow-up in 76% patients.47 Induction therapy in children is well tolerated and associated with higher glomerular filtration rate at 1 year without significant adverse events, but longer follow-up is advised.48

**Hepatitis C virus-seropositive recipients**

In hepatitis C virus-seropositive recipients who do not have advanced liver disease, kidney transplant is associated with better survival than staying on the transplant waiting list.49 However, the potentially increased immunosuppression with depleting than nondepleting induction agents may favor the progression of hepatitis C infection and cause adverse outcomes.50,51 Therefore, graft and patient survival after deceased-donor kidney transplant in hepatitis C virus-seropositive patients were compared in patients who received induction with depleting or nondepleting agents.52 Depleting and nondepleting agents were associated with similar frequency of graft and patient survival, both unadjusted and corrected for confounding variables. Graft and patient survival were similar with hepatitis C virus-seropositive and seronegative donors. Significant predictors of adverse graft outcomes included delayed graft function, donor death from stroke, African American recipients, dialysis duration per year, donor age per year, and recipient age per year (Table 1).52 Adverse patient outcomes were predicted significantly by delayed graft function, donor death from stroke, dialysis duration per year, and recipient age per year (Table 1).52 Therefore, deceased-donor kidney transplant from hepatitis C virus-seropositive donors to hepatitis C virus-seropositive recipients who do not have advanced liver disease may be justified and may alleviate the waiting list burden for deceased-donor kidney transplant. Furthermore, recipient...
hepatitis C virus-seropositivity may not affect the selection of induction agents used during kidney transplant.\textsuperscript{52}

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P ≤</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graft survival</td>
<td>Delayed graft function</td>
<td>1.48</td>
<td>(1.30 to 1.70)</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>Donor death from stroke</td>
<td>1.28</td>
<td>(1.11 to 1.48)</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>African American recipient</td>
<td>1.23</td>
<td>(1.07 to 1.41)</td>
<td>.003</td>
</tr>
<tr>
<td></td>
<td>Dialysis duration per year</td>
<td>1.02</td>
<td>(1.01 to 1.04)</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td>Donor age per year</td>
<td>1.01</td>
<td>(1.004 to 1.015)</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>Recipient age per year</td>
<td>1.009</td>
<td>(1.002 to 1.016)</td>
<td>.02</td>
</tr>
<tr>
<td>Patient survival</td>
<td>Delayed graft function</td>
<td>1.38</td>
<td>(1.15 to 1.67)</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>Donor death from stroke</td>
<td>1.33</td>
<td>(1.09 to 1.63)</td>
<td>.005</td>
</tr>
<tr>
<td></td>
<td>Dialysis duration per year</td>
<td>1.04</td>
<td>(1.02 to 1.06)</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>Recipient age per year</td>
<td>1.04</td>
<td>(1.03 to 1.05)</td>
<td>.001</td>
</tr>
</tbody>
</table>

\textsuperscript{52}Data adapted from Sureshkumar et al (2012).

Desensitization

New antibody-detection techniques (Luminex, Austin, TX, USA) show that 40\% of patients on the kidney transplant waiting list are presensitized by having HLA antibodies. In addition, HLA antibodies are present in all patients who lost a previous graft and await revision transplant.\textsuperscript{53} Antibodies against non-HLA antigens such as the angiotensin type 1 receptor may be present on graft endothelium, and this may impair graft outcome.\textsuperscript{54} Highly sensitized patients (percent patients on waiting list: United States, 14\%; Eurotransplant, 2\%) have ≥ 85\% serum panel reactive antibodies. Presensitized patients remain on the kidney transplant waiting list 2 to 3 times longer than nonsensitized patients.\textsuperscript{55} Some highly sensitized patients have a broad range of HLA antibodies that may preclude any acceptable organ from a potential donor, and these patients are at an increased risk of antibody-mediated rejection and kidney allograft loss, even when the crossmatch results are negative at transplant.\textsuperscript{56}

Desensitization protocols aim to lower donor-specific antibodies at transplant to safe levels. A minimum prerequisite for transplant is a negative complement-dependent cytotoxicity crossmatch at transplant.\textsuperscript{57} Even when the crossmatch is negative without desensitization, highly sensitized patients have decreased allograft survival, probably because of undetected donor-specific antibodies or increased alloreactivity. The Heidelberg algorithm combines various measures to overcome these problems with pretransplant plasmapheresis (1 session; deceased-donor transplant) or repeated immunoadsorption (living-donor transplant) and rituximab (375 mg/m\textsuperscript{2}) when all crossmatches are negative. Treatment after transplant may include repeated plasmapheresis (deceased-donor transplant) or immunoadsorption (living-donor transplant). After transplant, donor-specific antibody levels are monitored (days 0, 7, 30, and 180, and every 6 months) and protocol biopsies are performed (days 7 and 90).\textsuperscript{58}

Recipients who have a positive crossmatch with the prospective kidney donor are desensitized by removal of alloantibodies from the recipient’s circulation by plasmapheresis, immunoadsorption, or modulation of antibody responses by intravenous immunoglobulin alone or in combination with plasmapheresis.\textsuperscript{59} These approaches may be combined with the anti-CD20 antibody rituximab or the proteasome inhibitor bortezomib to deplete B lymphocytes or plasma cells and decrease the production of donor-specific antibodies.\textsuperscript{59,60} In addition, blocking the complement pathway with the complement C5 inhibitor eculizumab may prevent allograft damage when HLA antibodies bind to the kidney allograft endothelium.\textsuperscript{61}

There are few reports of conversion of a positive crossmatch in deceased-donor kidney recipients immediately before transplant. The desensitization protocols typically use plasmapheresis or immunoadsorption to ensure rapid antibody depletion before transplant, and potent immunosuppression for sustained reduction of donor-specific antibodies after transplant. Immunoadsorption is effective in the removal of HLA alloantibodies from highly sensitized kidney transplant candidates.\textsuperscript{62} In addition, immunoadsorption in combination with potent immunosuppression including antilymphocyte antibody therapy may be effective in highly sensitized recipients.\textsuperscript{63}

More HLA-mismatched transplants may be feasible because of the availability of effective options to treat highly sensitized kidney transplant recipients and patients who have a positive crossmatch with their donors. These options include sensitive antibody detection techniques, effective antibody elimination devices, and new therapeutic agents.\textsuperscript{64} Available options may be used in an integrated way to successfully transplant these high-risk recipients.\textsuperscript{65}

Delayed graft function

Delayed graft function is defined by the need for dialysis within 7 days after kidney transplant.
Delayed graft function is associated with adverse outcomes in kidney transplant including acute rejection, bacterial infections, decreased kidney function at 1 year as measured by creatinine clearance, and decreased allograft survival.66 There are nonimmunologic factors and immunologic factors that are associated with an increased risk of developing delayed graft function.67 Risk factors for delayed graft function may include older donors; cold ischemic time ≥ 24 hours; decreased creatinine clearance in the donor; and expanded-criteria donors.68

A risk-adjusted immunosuppressive program was developed to decrease the incidence of delayed graft function and acute rejection in high-risk patients and improve graft survival. The risk of developing delayed graft function may be decreased with use of rATG given before reperfusion.7 Outcomes were evaluated for 2 regimens in 2 patient groups that had similar recipient age, sex, race, body mass index, and duration of wait before transplant (Table 2). The immunosuppressive induction agents rATG or IL-2R antibody were associated with similar risks of delayed graft function. At 6 months after transplant, the mean creatinine level was higher and the creatinine clearance was lower in the rATG than IL-2R antibody group, but the frequency of biopsy-proven acute rejection was similar in the 2 groups (Table 2).69

The use of rATG in higher-risk recipients for DGF and AR did not significantly reduce the DGF rate. At 6 months the allograft function measured as creatinine clearance or serum creatinine was lower in the rATG group than patients who received anti-CD25 Ab induction. The choice of induction therapy may be improve outcomes in high-risk patients in the short-term study.68

Old donors

Patients aged > 65 years who have end-stage renal disease represent > 15% potential kidney transplant recipients.70 The use of organs from so-called “marginal donors” has been proposed for older recipients. Kidneys from extended-criteria donors or donors aged > 60 years commonly are allocated to older recipients.71 The combination of “marginal donors” and older recipients (“old-for-old”) requires a careful immunosuppressive strategy to avoid toxic and infectious complications and must consider comorbidities of older patients and the poorer quality of kidneys allocated to these recipients. Therefore, immunosuppression in older recipients is important for successful kidney transplant.72

A strong initial induction regimen has been proposed that includes the potent combination of rATG and basiliximab followed by minimal immunosuppressive maintenance.73 In a study of 46 patients who had deceased-donor kidney transplant from older donors (aged > 60 y) or younger donors (aged < 60 y), induction therapy with a combination of rATG (200 mg/d, intravenous, day 0-3) and basiliximab (20 mg, intravenous, day 0-4) was followed with maintenance immunosuppression starting on day 4 that included a low dose of a calcineurin inhibitor and steroids.73 At 6 months after transplant, the 2 groups had similar frequency of patient survival (younger, 100%; older, 95%), graft survival (younger, 96%; older, 95%), and acute rejection (younger, 8%; older, 0%). The older patients had significantly greater mean serum creatinine concentrations (younger, 132.6 ± 26.52 µmol/L [1.5 ± 0.8 mg/dL]; older, 167.96 ± 26.52 µmol/L [1.9 ± 0.3 mg/dL]; P < .0002), but the 2 groups had similar mean proteinuria (younger, 0.1 ± 0.1 g/24 h; older, 0.2 ± 0.1 g/24 h; g/24 h NS) and similar infectious, hematologic, and lymphoproliferative disorder complications.73 Therefore, a combination of rATG and basiliximab may provide effective and safe immunosuppression in old-for-old kidney transplant.

<table>
<thead>
<tr>
<th>Variable</th>
<th>High</th>
<th>Risk category</th>
<th>Low</th>
<th>P ≤†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>60</td>
<td>54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Rabbit antithymocyte globulin (rATG)</td>
<td>Interleukin 2 receptor (IL-2R) antibody</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold ischemia time (h)</td>
<td>23.7</td>
<td>17.6</td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td>Patients with cold ischemia time ≥ 24 h (%)</td>
<td>36.7%</td>
<td>13%</td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td>Mean length of hospital stay (d)</td>
<td>8.7</td>
<td>7.6</td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td>Creatinine at 6 mo after transplant (µmol/L/mg/dL)</td>
<td>132.6 ± 70.71 [1.5 ± 0.8]</td>
<td>114.92 ± 53.04 [1.3 ± 0.6]</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance at 6 mo (mL/min/mL/s)</td>
<td>55.2 [0.92]</td>
<td>68.4 [1.14]</td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td>Biopsy-proven acute rejection, frequency (%)</td>
<td>6.7%</td>
<td>13%</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

Data adapted from Foster et al (2012).69

†NS, not significant (P > .05).
with good kidney function and no increased risk of infectious or hematologic complications after transplant.\textsuperscript{73}

\textbf{Conclusions}

In 2011, the different agents used for induction immunosuppression for kidney transplant in the United States included T-cell-depleting antibodies (58%), IL-2R antibodies (22%), combination therapy with T-cell-depleting antibodies and IL-2R antibodies (4%), and none (17%).\textsuperscript{74} Current practice includes adjusting induction therapy based on risk-benefit considerations for each patient. The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines recommend induction therapy with a biologic agent as part of the initial immunosuppressive regimen in kidney transplant recipients (grade 1A recommendation).\textsuperscript{75} In addition, these guidelines recommend that an IL-2R antagonist be used as first-line induction therapy (grade 1B recommendation) and suggest the use of a lymphocyte-depleting agent and not an IL-2R antagonist for recipients that have high immunologic risk (grade 2B recommendation).\textsuperscript{75}

Many centers hesitate to use potent induction therapy because of the risks of infection or malignancy and unavailability of long-term data about graft survival. The choice of induction agent is controversial. Basiliximab may be preferred for low-risk patients and rATG may be preferred for high-risk patients (Table 2). Alemtuzumab also may be considered for low-risk patients, but a trial comparing basiliximab and alemtuzumab is required to assess efficacy and risks of cancer and infection. Rituximab and bortezomib may be useful in desensitization protocols combined with plasmapheresis, immunoabsorption, or intravenous immunoglobulin, but the long-term safety and efficacy of these regimens are unknown.

\textbf{References}


