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REVIEW

Selection of induction therapy in kidney transplantation

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Summary

Currently available immunosuppressive agents can be classified into three categories: induction agents, maintenance therapy, and treatment for rejection. This review article will focus on induction immunosuppression. There are three antibodies which are used for induction therapy: the lymphocyte-depleting agents – anti-thymocyte globulin and alemtuzumab, and basiliximab which is nondepleting. Historically, immunosuppressant selection was solely based on efficacy for prevention of rejection. In the current era of transplantation, it is now common practice in the transplant community to select induction therapy on the basis of risk–benefit considerations for each patient. This article will focus on the efficacy of available induction agents and the selection of induction agent based on donor and recipient risk factors.

Introduction

The main goal of immunosuppression is to prevent allograft loss without the consequences of infection or toxicity. The primary reason for the use of induction therapy, or intense immunosuppressive therapy at the time of transplant, is to avoid early acute rejection historically known to predict graft loss. The choice of induction agent varies from country to country, center to center, and patient to patient. Since the late 1990s, the use of OKT3 and horse ATG (eATG) has declined, while the use of rabbit ATG (rATG) and basiliximab has increased (Fig. 1). Lymphocyte-depleting agents are the most commonly used agents for induction (54%), followed by nondepleting agents (24%) based on US data from 2009, while in other countries choice of induction agent varies [1]. Selection of induction therapy on the basis of risk–benefit considerations is becoming more common. This review will consolidate the published evidence of trials addressing the effectiveness and safety of induction therapy in transplantation and selection of induction agent based on donor and recipient risk factors. Table 1

Pharmacology

Currently, the three most commonly used antibodies are basiliximab, ATG, and alemtuzumab. Basiliximab, the only FDA-approved induction agent in renal transplantation, is an interleukin-2 receptor antagonist (IL-2RA). It is dosed as a bolus of 20 mg intraoperatively and 4 days following transplantation (Table 2). Currently, there are four commercially available preparations of ATG (Table 3). Equine

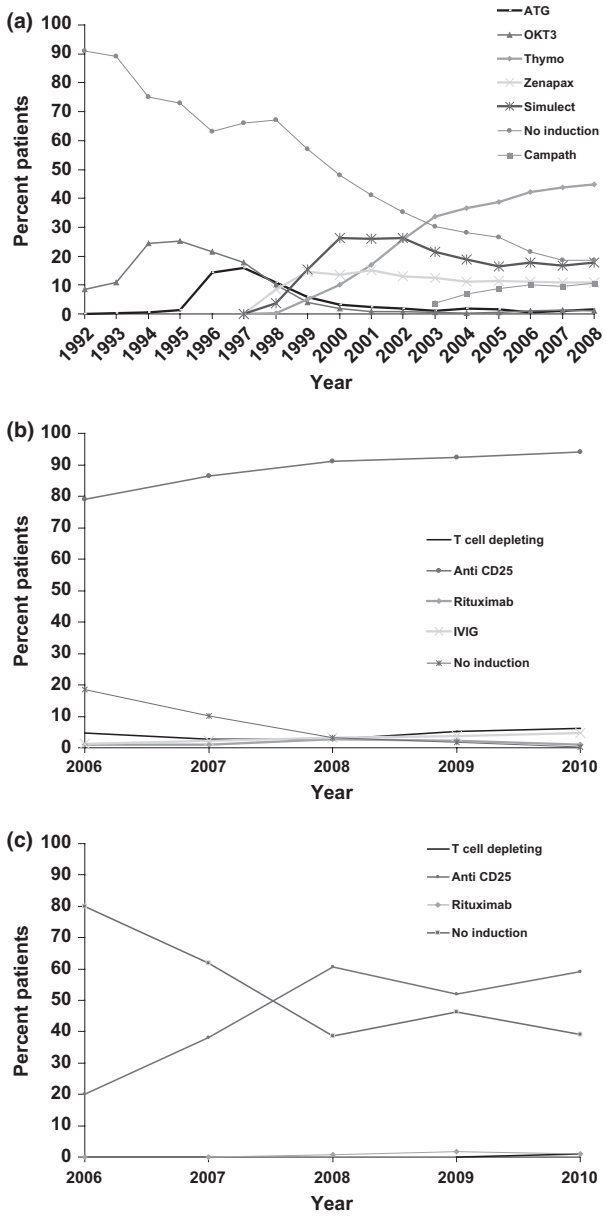

Figure 1 Trends in (a) US, (b) Australian and (c) New Zealand kidney transplantation induction immunosuppression.

ATG has been largely replaced by rATG which is better tolerated and more efficacious for both the prevention and treatment of rejection [2–5]. Although ATG is not currently FDA approved as induction therapy for kidney transplantation in the USA, it is the most commonly administered agent for this purpose. Induction doses range from 1–6 mg/kg/dose over 1–10 days with a more typical regimen of 1.5 mg/kg for 3–5 days [2,6–14]. In animal models, higher initial doses of shorter duration approximating a human-equivalent dose of 6 mg/kg were associated with more peripheral and central lymphocyte depletion and better allograft survival [15]. In addition to depleting harmful T cells, ATG may balance T-regulatory memory cells [16–19]. Total higher doses may not be necessary as proven in one study where a mean total dose of 5.7 mg/kg was shown to produce similar outcomes in high-risk recipients who received an average of 10.3 mg/kg [7]. Higher cumulative doses and prolonged duration of induction agents are thought to be associated with an increased risk of infection and the potential development of lymphoma, while low doses <3 mg/kg may not effectively prevent acute rejection [20]. With ATG, thrombocytopenia and leukopenia are common and should result in subsequent dose adjustment [21]. CD2 and CD3 counts may also be used in determining the need for dose adjustment. As of September 2012, alemtuzumab is no longer commercially available but is provided by its manufacturer through a special program. It was FDA approved for B-cell chronic lymphocytic leukemia, however, it has been used off label for induction therapy and in the treatment of acute rejection in transplantation [22]. It is given intravenously as a one-time dose of 30 mg over 2 h. The subcutaneous route has also been studied, although this method of administration is not FDA approved [23].

Adverse events

In general, there are few adverse events associated with basiliximab although, rare, severe hypersensitivity reactions, including anaphylaxis, have been reported in patients with murine or mannitol hypersensitivity. Adverse events, including cytokine-release syndrome, leukopenia, and thrombocytopenia, are more common with rATG and alemtuzumab. Peripheral administration of ATG may lead to venous thrombosis but can be reduced with concomitant hydrocortisone and heparin in the infusion solution [24,25]. Other less frequently occurring adverse events of ATG include hives (with eATG), serum sickness, and anaphylaxis. Serum sickness is caused by delayed immunologic reaction to nonantibody proteins contained in the rabbit serum preparation [26] and may be associated with previous rabbit exposure [27]. Unlike anaphylaxis, the onset of primary serum sickness is delayed with respect to administration of rATG, and may occur between 6 and 21 days following dosing. In two separate noncomparative studies of rATG, serum sickness occurred in 7.5% [28] and 10.6% of patients [29], respectively. The early use of alemtuzumab in renal transplant recipients was associated with intense and prolonged lymphocyte depletion, increased late antibody-mediated graft rejection, and increased rates of serious infection [29–32].

Malignancy

Using registry databases, three published studies have explored the association of induction agents with the

Table 1. Inductions agents and FDA-approved indications.

Generic	Brand	Classification	FDA indication	FDA approval	Manufacturer
Basiliximab	Simulect	IL-2 receptor blockers, monoclonal antibody, CD25	Prevention of acute rejection in kidney and liver transplantation	1998	Novartis (East Hanover, New Jersey, US)
Daclizumab	Zenapax	IL-2 receptor blockers, monoclonal antibody, CD25	Prevention of acute rejection in kidney transplantation	1997–2009*	Roche
Rabbit anti-thymocyte globulin	Thymoglobulin	Polyclonal anti-T cell	Treatment of acute rejection in kidney transplantation	1998	Genzyme-Sanofi (Bridgewater, New Jersey, US)
Horse anti-thymocyte globulin	ATGAM	Polyclonal anti-T cell	Treatment of acute rejection in kidney transplantation Treatment of moderate to severe aplastic anemia in patients who are unsuitable for bone marrow transplantation	1981	Pfizer (New York, US)
Alemtuzumab	Campath	Monoclonal antibody, CD52	Treatment of B-cell chronic lymphocytic leukemia (B-CLL)	2001–2012*	Berlex Laboratories (Montville, New Jersey, US)
Muromonab, OKT3	Orthoclone	Monoclonal antibody, CD3	Treatment of acute rejection in kidney, heart, or liver transplantation	1986–2009*	Janssen-Cilag

*Withdrawn from the market.

Table 2. Inductions agents – dose and adverse effects.

Generic	Dose	Premedications	Dosing adjustment	Adverse effects
Basiliximab	20 mg IV × 2 doses	None	Pediatrics (<35 kg give 10 mg)	Hypersensitivity reactions (rare)
Rabbit anti-thymocyte globulin	1.5 mg/kg IV × 3–14 days	Yes	Decrease dose by one-half if the white cell count is between 2000–3000 cells/mm^3, or if the platelet count is between 50 000 and 75 000 cells/mm^3 Discontinue when white blood cell or platelet counts fall below the lower limits of these ranges	Rash, infusion reaction, thrombocytopenia, leukopenia, serum sickness, anaphylaxis (rare)
Horse anti-thymocyte globulin	15 mg/kg IV × 3–14 days	Yes	Adjust dose for leukopenia and thrombocytopenia	Rash, infusion reaction, thrombocytopenia, leukopenia, hives, serum sickness, anaphylaxis (rare)
Alemtuzumab	30 mg IV × 1 dose	Yes	Adjust for neutropenia	Infusion reaction, leukopenia

IV, intravenous.

Table 3. Polyclonal anti-thymocyte globulin comparisons.

	Atgam	Lymphoglobuline	Thymoglobulin	ATG-Fresenius
Manufacturer	Pfizer	Various	Genzyme-Sanofi	Fresenius-Biotech GmBH
Location	New York, USA		Cambridge, USA	Gräfelfing, Germany
Species	Horse	Horse	Rabbit	Rabbit
Concentration (mg/ml)	50	10–20	5	20
Immunogen	Human thymus	Human thymus	Human thymus	Jurkat lymphoblastic cell line
Dosage per day (mg/kg)	10–30	10	1.25–2.5	1–5

development of post-transplant malignancy [33–35]. These three studies reported varying results (Table 4.) In addition to the inherent limitations of registry databases analyses, it is important to note other weaknesses. First, rATG and IL2-RAs were not approved and commonly used until 1998–1999 and therefore, a majority of these meta-analyses focus on the use of OKT3 and various preparations of ATG. Second, additional selection bias may have occurred,

Table 4. Meta-analysis of induction agent and malignancy.

Source	Number of patients	Dates studied	Result	Reference
SRTR	41 686	12/95 to 2/02	Any antibody* versus no antibody and PTLD (RR = 1.78, $P < 0.001$), but not with *de novo* tumors (RR = 1.07, $P = 0.42$). PTLD and rATG versus no antibody (RR = 3.00, $P = 0.001$) but not with horse ATG-treated patients (RR = 1.50; $P = 0.10$)	[33]
Medicare Claims	25 127	1996–2000	The risk factors associated with PTLD included recipient age <20 years, recipient history of pretransplant malignancy and malignant cause of end-stage renal disease, level of HLA matches, and OKT3 or ATG therapy. When analyzed separately, rATG ($n = 684$) was not associated with increased risk of PTLD, $P = 0.37$	[34]
USRDS	38 519	1997–2000	A 72% increase in risk of PTLD associated with monoclonal antilymphocyte induction versus no induction antibody use ($P = 0.03$). In contrast, there was not increase in risk associated with polyclonal agents (29%; $P = 0.27$) or IL-2R antagonists (14%; $P = 0.52$)	[35]

PTLD, post-transplant lymphoproliferative disorder; RR, relative risk; SRTR, Scientific Registry of Transplant Recipients; USRDS, United States Renal Data System

*Atgam, thymoglobulin, OKT3, daclizumab, basiliximab, Nashville rabbit ATG/ALG, T10B9.

as it is common to use polyclonal antibodies in high-risk patients. Furthermore, transplantation has evolved over the years and medical management of the recipients has changed, including the routine use of antiviral prophylaxis, which has been shown to reduce the risk of post-transplant lymphoproliferative disorder.

Pharmacoeconomics

Only a few trials have evaluated the cost-effectiveness of antibody induction. They have compared rATG with eATG [36], basiliximab with placebo [37], and basiliximab with rATG [38]. Basiliximab may offer an economic advantage to rATG based on the lower initial hospital stay duration and number of infectious episodes [38]. Direct present day well-designed pharmacoeconomic comparisons of the agents are needed.

Efficacy

A recent analysis of United Network for Organ Sharing (UNOS) registry data showed that induction with any agent leads to better outcomes than no induction therapy at all [39]. The efficacy of individual agents is discussed below.

Basiliximab versus no induction

Basiliximab has demonstrated a statistically significant reduction in the incidence of acute rejection in three major clinical trials, which used a maintenance regimen of cyclosporine and corticosteroids with and without an antimetabolite [40,41]. A trend toward reduced rejection (15.3% basiliximab vs. 26.6% placebo), has also been reported using a more contemporary regimen [cyclosporine, corticosteroids, and mycophenolate mofetil (MMF)] in the treatment group, although it did not reach statistical significance [42]. Likewise, a retrospective analysis from the SRTR (Scientific Renal Transplant Registry) of primary kidney transplant recipients ($n = 28\ 636$) initially on a regimen of prednisone, tacrolimus, and mycophenolic acid demonstrated a small but significant difference in acute rejection at 1 year in the IL-2RA group (11.6%) versus no induction (13.0%; $P = 0.001$) [43]. None of these studies demonstrated a difference in patient or graft survival.

In a meta-analysis, 14 trials enrolling 2410 patients compared IL-2RAs with placebo and found reduced acute rejection rates at 1 year (RR 0.67, CI 0.60–0.75), but the incidence of graft loss was the same [44]. The authors concluded that given a 40% risk of rejection, seven patients would need treatment with IL-2RA in addition to standard therapy, to prevent one patient from rejection, with no improvement in graft or patient survival.

Anti-thymocyte globulin versus no induction

Two short-term randomized trials of deceased donor recipients have demonstrated a reduced rejection rate with rATG [29,45]. In the first 6 months, patients treated with rATG - tacrolimus had the lowest incidence of biopsy-proven acute rejection (BPAR 15.1% vs. 21.2% rATG – cyclosporine microemulsion, $P = 0.177$; vs. 25.4% tacrolimus – no induction, $P = 0.004$). The rATG-cyclosporine microemulsion group may have been considered higher risk because there were more patients with high panel reactive antibody (PRA) ($P = 0.044$) and previous transplants ($P = 0.03$). Both trials demonstrate that use of ATG induction lowers the incidence of early acute rejection, but at the expense of reversible leukopenia, thrombocytopenia, and infection, particularly cytomegalovirus (CMV). This raises the ques-

tion of whether costly CMV prophylaxis should routinely be given to patients who receive rATG induction. Furthermore despite the improvement in rejection rates; patient survival, graft survival, and renal function were similar. In addition, caution should be exercised when extrapolating these trials to other populations given the low-risk study population in both trials.

Anti-thymocyte globulin versus basiliximab

A recent meta-analysis of six randomized studies including 853 patients showed no differences between ATG and basiliximab for the outcomes including BPAR, delayed graft function (DGF), graft loss, and patient death [46]. A major limitation to this meta-analysis was that authors included all preparations of ATG in the analysis. In one of the individual trials in which eATG was used ($n = 135$), basiliximab and early initiation of cyclosporine therapy resulted in acute rejection rates similar to those achieved with eATG and delayed cyclosporine [47]. In two other trials included in the meta-analysis ($n = 135$), rATG – Fresenius resulted in similar acute rejection rates to basiliximab [48,49]. The remaining three studies that included rATG and basiliximab and yielded different results as described below.

Basiliximab and rATG (1.0–1.5 mg/kg started within 24 h for 6–10 days) were studied in a randomized, multicenter, European study ($n = 100$) [50]. In addition to MMF and corticosteroid that were later withdrawn, microemulsion cyclosporine was administered on day 0 or 1 in the basiliximab group and delayed until the serum creatinine fell below 2.7 mg/dl (days 6–10) in the rATG group. CMV prophylaxis was not utilized. At 12 months, fever and leukopenia were seen more commonly in the rATG arm, while incidence of BPAR (8%) and serum creatinine were similar. There were fewer CMV infections in the basiliximab group ($P = 0.005$), but the rate of clinically significant CMV cases was not different. In 5-year follow-up, outcomes remained comparable [51]. Limitations of the trial include that immunosuppression was not administered optimally; the early initiation of cyclosporine and possibility of delaying rATG for up to 24 h after transplantation may have favored the basiliximab arm. In addition, although one of the primary endpoints was the incidence of viral infections, the study was not stratified by CMV serostatus and the rATG group contained more recipients at a higher risk for CMV infection. In addition to being underpowered, the exclusion of high immunologic risk patients may have introduced selection bias.

The timing of cyclosporine initiation was addressed in a subsequent, small, randomized, multicenter, 1-year European study that compared basiliximab ($n = 52$) versus rATG (1 mg/kg on day 0 and 1, subsequent doses given to maintain CD3+ counts $<20/mm^3$, $n = 53$) [52]. The rATG group received a mean of 5.4 infusions. Unlike the previous trial, cyclosporine microemulsion was initiated in both groups when the serum creatinine level dropped below 2.3 mg/dl, which occurred on average at day 6–7 postoperatively. Corticosteroids (with potential for withdrawal) and MMF were given and CMV donor seropositive/recipient seronegative patients received valacyclovir. Like the previous trial, high immunologic risk patients (PRA >20% and history of previous graft survival <1 year) were excluded. The study, powered to detect a difference in adverse events, showed higher rates of CMV infection, leukopenia, and thrombocytopenia in the rATG group. All other outcomes were similar; however, the study was not powered to address efficacy and therefore the question still remains whether or not there is truly a difference between basiliximab and rATG in low immunologic risk patients.

In contrast, results of the larger, third trial, using moderate to high-risk deceased donor recipients, demonstrated an improved composite endpoint of the incidence of rejection, graft loss, and patient death that favored rATG (19.1% vs. 31.6%; $P = 0.01$) [53,54]. Patients were randomized to rATG (1.5 mg/kg days 0–4, first-dose prereperfusion) or basiliximab in this multicenter international trial ($n = 277$) and maintained on a regimen of cyclosporine microemulsion, MMF, corticosteroids, and CMV prophylaxis. At a mean of 10 months of follow-up, the estimate of combined endpoint was 19.1% in the rATG arm and 31.6% in the basiliximab arm ($P = 0.01$), with acute rejection being the driving factor (14.2% rATG vs. 25% basiliximab, $P = 0.013$). The incidence of leukopenia, was higher in the rATG treatment arm (42.6% vs. 6.6%; $P < 0.0001$). However, the incidence of CMV was not different (7.1% rATG vs. 13.2% basiliximab; $P = 0.09$). Five-year follow-up demonstrates that the incidence of acute rejection requiring antibody rescue remained lower in the rATG group (3% vs. 12%, $P = 0.05$).

Alemtuzumab

A few, randomized trials of alemtuzumab have been published [55–59]. The most noteworthy is a large, multicenter, 3-year, randomized trial that stratified patients by rejection risk: low-risk (alemtuzumab vs. basiliximab, $n = 335$) or high-risk (alemtuzumab vs. rATG, $n = 139$) [59]. All patients received tacrolimus, MMF, and early steroid withdrawal. The rate of BPAR was significantly lower in the alemtuzumab group than in the conventional-therapy group (low- and high-risk combined - 13% vs. 20%, $P = 0.03$). However, this benefit did not translate to improved graft survival or improved renal function. In addition, the apparent superiority of alemtuzumab was restricted to low-risk patients (BPAR 10% vs. 22%, $P = 0.003$). Among high-risk patients, alemtuzumab and

rATG had similar efficacy (BPAR 18% vs. 15%; $P = 0.53$). In both the low- and high-risk groups, there was a trend toward late rejection in the alemtuzumab arm, an observation reported in several other studies.

Different results were seen in a large, single-center study that compared alemtuzumab with rATG ($n = 222$) in low- and high-risk kidney alone, kidney-pancreas, pancreas after kidney or pancreas alone transplants [58]. Patients were randomized based on immunologic risk with 35 percent of the patients considered high risk (current PRA >20%, retransplant, African American, or <40 years of age). In the 180 kidney transplant recipients, BPAR episodes occurred in 14% of alemtuzumab patients compared with 26% of rATG patients ($P = 0.02$), with no difference between low- and high-risk patients (low risk - 13% alemtuzumab vs. 24% rATG, $P = 0.08$; high risk - 17% alemtuzumab vs. 29% rATG, $P = 0.1$). Importantly, the study used a regimen of alternate-day rATG dosing rather than standard daily dosing and tacrolimus levels were lower at 5 days post-transplantation in the rATG group (4.1 vs. 5.7 mg/dl, $P = 0.01$); likely contributing to higher rejection rates than other trials involving daily rATG and prompt initiation of tacrolimus.

A total of 808 participants from six randomized controlled trials were included in a recent meta-analysis of alemtuzumab. Alemtuzumab was associated with lower incidence of BPAR over traditional antibodies (RR 0.63, CI 0.45–0.87, $P = 0.005$). This difference remained when only studies comparing alemtuzumab with rATG were included (RR 0.32, CI 0.11–0.91, $P = 0.03$), but lost significance when only patients at high-risk were included (RR 0.86, CI 0.48–1.55, $P = 0.62$). The lower rejection rates did not translate into an increase in graft or patient survival [60].

Patient and Donor Characteristics

Antibody induction is effective in preventing acute rejection, but its effects on long-term renal allograft function, infection rates, and cancer rates remain controversial especially in low-risk patient populations. It is now common to select induction therapy on the basis of risk–benefit considerations for each patient. Recent guidelines recommend that an IL2-RA be the first-line induction therapy and suggest the use a lymphocyte-depleting agent for recipients at high immunologic risk [61]. Risk factors for acute rejection are listed in Fig. 2. Available evidence on patient and donor risk factors is reported below.

Live donors

A recent OPTN/UNOS database analysis of adult living donor kidney recipients compared antibody use (IL-2RA and ATG) with no induction in two cohorts; an earlier era (1998–2002; $n = 21{,}919$) and a later era (2003–2008, $n = 26{,}837$). Acute rejection decreased overall from 1998 to 2008 (18.5% to 8%); however, induction use was not associated with decreased rejection at 6 or 12 months in the most recent era and did not influence patient or graft survival in either era. Unfortunately, this study did not analyze the type of induction agent used [62].

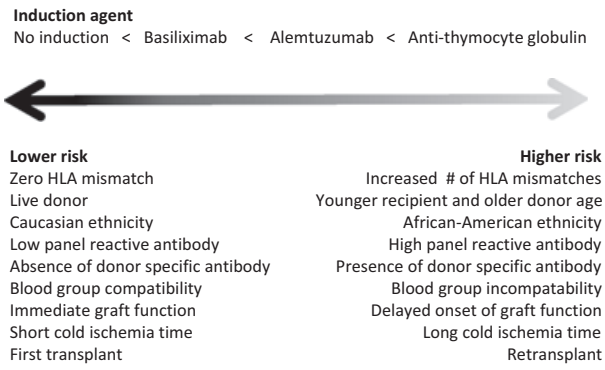

Figure 2 Induction therapy choice based on risk assessment.

Studies that have compared no induction to individual agents, including ATG, IL-2RA, and alemtuzumab, have produced different results. Rabbit ATG appears to be safe and effective in live-donor kidney transplantation [63–65]. This was shown in a single-center study in which, compared with a national control group with no induction, rATG use provided superior 5-year patient survival (96% vs. 90%, $P = 0.0326$), allograft survival (82 vs. 79%, $P = 0.0901$), and 1-year acute rejection rate (2% vs. 21%, $P < 0.001$) [63]. Another trial at a single institution in live unrelated kidney recipients showed that the use of rATG was associated with a significant reduction in acute rejection rates (2% vs. 48%, $P < 0.001$) in the first post-transplant year [64]. Similar results have been seen in an Australian/New Zealand database, where IL-2RA resulted in a 51% reduction in the incidence of acute rejection ($P < 0.001$) and reduced overall graft loss (HR = 0.58, 95% CI: 0.35–0.96; $P = 0.03$) compared with no induction [66]. Lower acute rejection rates were also seen with alemtuzumab in a recent study where transplants who received alemtuzumab had a lower rate of rejection than an historical control without induction at 1 year, 6.8% vs. 17.0%, $P < 0.05$, respectively [67].

Direct comparisons have been reported in a database study of live-donor kidney transplants performed from 2003 to 2006 [68]. The incidence of acute rejection at discharge was lower in the alemtuzumab group when compared with that in the IL-2RA group (0.8% vs. 4.4%, respectively, $P < 0.001$), but it was similar by 1 year post-transplant (9.8% vs. 11%, respectively). After adjusting for confounding factors, the alemtuzumab group had a higher risk of graft loss (HR 1.23, 95% CI: 1.03–1.48) at 4 years with comparable patient survival.

Only a few prospective induction trials of live-donor transplant recipients have been performed [69,70]. In a single-center trial in Egypt, live-donor recipients received either basiliximab ($n = 50$) or no induction ($n = 50$) in conjunction with steroids, cyclosporine micro-emulsion, and azathioprine. Basiliximab reduced the incidence rejection by 26% at 1 year, however, patient and graft survival were similar at 10-years follow-up.

Antibody induction may have a positive role in live-donor transplant recipients who undergo corticosteroid withdrawal [71]. When early corticosteroid withdrawal was employed in living donor recipients, recipients receiving ATG had a similar incidence of acute rejection at six months compared with recipients receiving maintenance corticosteroids without antibody induction.

Zero-mismatch deceased donor kidney recipients

Like live-donor transplant recipients, zero antigen mismatched deceased donor kidney transplant recipients are considered to be at a lower risk for acute rejection. A recent database analysis explored the use of induction agents (rATG, IL2-RA, or alemtuzumab) versus no induction in this patient population and found that antibody induction was associated with a decreased risk of rejection at 6 months post-transplant, but this did not translate into improved graft and patient survival over the follow-up period (median 834 days) [72].

Standard criteria donor kidneys

Although conflicting, there is some evidence that compared with basiliximab, rATG may also be most beneficial in patients who receive a normotensive, standard criteria deceased donor kidney. A subset analysis of a randomized controlled study of rATG compared with basiliximab showed that recipients of a normotensive, standard criteria donor kidney treated with rATG had less acute rejection, death, and a composite endpoint defined by death, graft loss, or acute rejection than their counterparts treated with basiliximab [4].

Delayed graft function

Intraoperative administration may minimize ischemia-reperfusion injury and the subsequent development of DGF, a predictor of poor graft outcome [2,48,73]. Historically ATG was administered postoperatively, but the results of a prospective, randomized trial of deceased donor recipients revealed that compared with postoperative administration, intraoperative first-dose administration of rATG was associated with less DGF (14.8% intraoperative vs. 35.5% postoperative; $P < 0.05$) and significantly better renal function on day 14 (serum creatinine 1.81 vs. 2.82 mg/dl; $P = 0.04$) [20]. In addition, the length of hospital stay was shorter in patients who received the first dose of rATG intraoperatively (7.5 vs. 11 days; $P = 0.02$) and at six months of follow-up there was a nonsignificant trend toward lower acute rejection (3.6% intraoperative vs. 16% postoperative; $P = 0.11$). Other literature does not support the hypothesis that rabbit ATG directly prevents DGF [53]. Even if induction agents do not directly prevent DGF, the reduced risk of acute rejection may minimize the consequences of DGF.

Ethnicity

Retrospective data have not demonstrated a difference in outcomes depending on the type of induction therapy used in African American patients [74–77]. In a retrospective cohort study of kidney transplant patients in the USRDS from 2000 through 2005, patient and graft survival were similar in African American and Caucasian recipients of kidney transplantation using either rATG or IL-2RA [78]. Yet, IL-2RA may not be effective in preventing rejection for all patient populations, as shown in a recent study of Chinese renal transplant recipients ($n = 278$) [79]. After adjusting potential covariates, IL-2RA use provided no benefit on BPAR.

Immunosuppression minimization: steroid withdrawal regimens

There is sufficient evidence to support ATG use in low immunologic risk recipients receiving corticosteroid-free maintenance regimens [80–82]. Anti-thymocyte globulin has been proven to reduce acute rejection episodes when compared with no induction in a randomized corticosteroid withdrawal trial [83]. In one randomized study of rATG and early corticosteroid withdrawal, the TRIMS trial, the incidence of acute rejection was lower in the rATG induction arm (13.9% vs. 19.4% no induction, $P = 0.09$) [71]. It is important to note that only live-donor kidney transplant recipients were studied in this trial.

Rabbit ATG has been compared with basiliximab in patients receiving MMF, tacrolimus, and early corticosteroid withdrawal [84]. In this single-center, retrospective, cohort study of 99 consecutive patients, rATG patients had less acute rejection (7%) than patients who received basiliximab (26%) and the average time to first BPAR was longer in the rATG group, $P < 0.01$. Similar findings were observed in a retrospective cohort study ($n = 167$) in Brazil where fewer episodes of acute rejection were seen at 1 year in patients treated with rATG as compared with anti-IL2R (25.6% vs. 11.4%, $P = 0.01$) and at 5 years, a significantly reduced graft survival was observed in IL-2RA compared

with rATG patients (83.5% vs. 95.5%, $P = 0.01$) [85]. Multivariate analysis revealed that antibody induction was independently associated with patient and graft survival at 5 years (OR = 0.213, 95% CI: 0.046–0.991, $P = 0.04$).

Although many questions still remain unanswered with regard to steroid withdrawal, these trials demonstrate the possibility of safely withdrawing corticosteroids with the aid of rATG induction. One question is which patients are ideal candidates for withdrawal. As described above, early corticosteroid withdrawal is usually attempted in patients at low risk for acute rejection. In fact, one study has identified repeat transplantation, high PRA (>25%), African American race, DGF, diabetes, and Class II histocompatibility mismatches as significant risk factors for the development of acute rejection following early corticosteroid cessation [86]. Notably, in the same study, rATG induction therapy was identified as a factor that significantly reduced the odds of developing acute rejection (OR = 0.61; 95% CI: 0.30–1.27). The use of rATG and corticosteroid withdrawal in high-risk patients has not been studied in randomized trials, while retrospective studies have demonstrated some promise.

Recipient age

Elderly transplant recipients are at a greater risk for post-transplant complications because of an increased risk of infection, decreased immunoreactivity, and greater likelihood of receiving a high-risk donor organ. An OPTN/UNOS database review compared induction in elderly, deceased donor transplant recipients with alemtuzumab ($n = 1465$), rATG ($n = 7140$), and IL-2RA ($n = 6215$) between 2003 and 2008 [87]. The study compared recipients based on their risk for acute rejection and concluded that rATG use may be preferable among high-risk recipients (PRA >20%, prior transplant, black race) with high-risk donors (ECD, DCD, CIT >24 h), and possibly low-risk recipients with high-risk donors. This study was a database analysis, not a randomized trial, and therefore is susceptible to multiple biases. Very few studies have addressed the selection of induction agent in pediatric patients [88,89].

Conclusion

Basiliximab and rATG have a proven safety and efficacy profile for induction therapy in kidney transplantation. Further studies comparing rATG with the anti-IL2R antibodies will help to individualize regimens by aligning the choice of induction agent with the risk profile of each transplant recipient. It is now common practice in the transplant community to select induction therapy on the basis of risk–benefit considerations for each patient primarily based on epidemiologic and immunologic considerations. Despite these new recommendations, there are many unanswered questions relating to the use of potent induction agents. Induction agents have been associated with increased short-term costs and may contribute to an overall increased immunosuppressive state. Many centers are hesitant to use potent induction therapy because of the risks of infection or malignancy and lack of long-term data demonstrating a graft survival benefit. The choice of an induction agent remains debatable. However, basiliximab may be preferred for low-risk patients while rATG may be preferred for high-risk patients. Alemtuzumab has also shown promise in low-risk patients, but a prospective trial comparing basiliximab to alemtuzumab should be conducted to assess efficacy, the risk of cancer, and infection. Future research is needed to determine the ideal induction agents for specific patient populations. Further evaluation of induction in immunosuppression minimization regimens is required to determine their use in withdrawing either corticosteroids or potentially nephrotoxic calcineurin inhibitors.

Authorship

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