

# Induction Therapy for Kidney Transplant Recipients: Do We Still Need Anti-IL2 Receptor Monoclonal Antibodies?

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**Induction therapy with antilymphocyte biological agents is widely used after kidney transplantation, most commonly T lymphocyte-depleting rabbit-derived antithymocyte globulin (rATG) or an IL-2 receptor antagonist (IL2RA). Early randomized trials showed that rATG or IL2RA induction reduces early acute rejection, prompting recommendations by Kidney Disease Improving Global Outcomes that IL2RA induction be used routinely in first-line therapy after kidney transplantation, with lymphocyte-depleting induction reserved for high-risk cases. These studies, however, mainly used outdated maintenance regimens. No large randomized trial has examined the effect of IL2RA or rATG induction versus no induction in patients receiving tacrolimus, mycophenolic acid and steroids. With this triple maintenance therapy, the addition of induction may achieve an absolute risk reduction for acute rejection of only 1–4% in standard-risk patients without improving graft or patient survival. In contrast, rATG induction lowers the relative risk of acute rejection by almost 50% versus IL2RA in patients with high immunological risk. These recent data raise questions about the need for IL2RA in kidney transplantation, as it may no longer be beneficial in standard-risk transplantation and may be inferior to rATG in high-risk situations. Updated evidence-based guidelines are necessary to support clinicians deciding whether and what induction therapy is required for their transplant patients today.**

**Abbreviations:** ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; AR, acute rejection; ATG, antithymocyte globulin; BPAR, biopsy-proven

acute rejection; CI, confidence interval; CsA, cyclosporine; IL2RA, IL-2 receptor antagonist; KDIGO, Kidney Disease Improving Global Outcomes; MPA, mycophenolic acid; OPTN, Organ Procurement and Transplant Network; rATG, rabbit antithymocyte globulin; RR, relative risk; SRTR, Scientific Registry of Transplant Recipients

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## Introduction

The immunosuppressive regimen after kidney transplantation typically includes initial induction with an antilymphocyte biological agent, usually either a T lymphocyte-depleting agent or an IL-2 receptor antagonist (IL2RA). The primary aim of induction therapy is to reduce the risk of acute rejection. Lymphocyte-depleting agents have been used since the 1980s: murine anti-CD3 monoclonal antibody muromonab-CD3, which is no longer used, and polyclonal antithymocyte globulins (ATGs) derived from rabbit (rATG) or equine cell lines. In the 1990s, two nondepleting chimeric mAbs directed against the IL-2 receptor were introduced: basiliximab and daclizumab (the latter was later withdrawn). Currently, lymphocyte-depleting agents (most frequently rATG) are used in the majority (≈60%) of kidney transplantations in the United States, with IL2RA induction being used in ≈20% of cases (1). In contrast, in Europe, IL2RA induction is more widely used than rATG or other depleting agents (2). Other induction therapies used include the humanized anti-CD52 mAb alemtuzumab. Alemtuzumab has never been licensed for use in organ transplantation in any market, and its use in this setting remains off label; therefore, we will not discuss it in this paper and will focus on rATG and IL2RA induction.

A series of trials has demonstrated that induction therapy with ATG or IL2RA induction reduces the risk of early acute rejection episodes after kidney transplantation versus controls (3,4). In 2010, the Cochrane Collaboration published a meta-analysis of randomized controlled trials that compared IL2RA induction with placebo and with ATG (4). Biopsy-proven acute rejection (BPAR) rates

were  $\approx 30\%$  lower with IL2RA versus placebo (1-year relative risk [RR] 0.72, 95% confidence interval [CI] 0.64–0.81) and graft loss was reduced (1-year RR 0.75, 95% CI 0.62–0.90). In the total cohort, consisting primarily of recipients at low immunological risk (72% being first transplants), ATG was no more effective in preventing rejection than IL2RA agents, and the safety profile favored IL2RA induction. Based largely on these findings, the 2009 Kidney Disease Improving Global Outcomes (KDIGO) guidelines for the care of kidney transplant patients recommended (i) that induction therapy with a biological agent be a routine part of the initial immunosuppressive regimen (grade 1B) and (ii) that an IL2RA agent be the first-line therapy (grade 1B). KDIGO further recommended that lymphocyte-depleting agents be used selectively in patients at high immunological risk (grade 2B) (5). KDIGO defined high immunological risk as the following conditions: high number of HLA mismatches, younger recipient age, older donor age, black ethnicity (in the United States), panel reactive antibodies  $>0\%$ , presence of a donor-specific antibody, blood group incompatibility, delayed onset of graft function and cold ischemia time  $>24$  h. It is important, however, to consider the details of the studies that led to the development of these guidelines, such as the maintenance immunosuppressive regimen that was used. In view of recent evolutions in transplant care, it may be time to reassess the role of induction therapy following kidney transplantation.

#### **Induction therapy in standard-risk transplants**

The Cochrane meta-analysis (4), which underpinned the current KDIGO recommendations, included studies that were conducted mostly in the 1990s and early 2000s using maintenance regimens that have since been superseded. For the studies comparing IL2RA and no induction, 87% of patients received cyclosporine (CsA) rather than tacrolimus, only 50% received mycophenolic acid (MPA), 28% received azathioprine and 22% were treated with double rather than triple maintenance therapy. CsA has generally been replaced by tacrolimus as the calcineurin inhibitor of choice (1) after reports of lower rejection rates with tacrolimus (6,7). The use of azathioprine has typically been replaced by MPA for similar reasons (1,7). Most transplant centers now administer triple maintenance therapy with steroids, tacrolimus and MPA as the standard maintenance treatment (1), a shift that may in part explain the marked decrease in 1-year acute rejection rates from  $\approx 50\%$  in the early 1990s to  $\approx 10\text{--}15\%$  now (1,7,8). With this low basal level of acute rejection risk, the question arises of whether addition of induction therapy still offers an additional benefit in standard-risk kidney transplant recipients.

In fact, no large randomized trial has examined the effect of a classical scheme of either IL2RA or ATG induction versus no induction in patients receiving tacrolimus and MPA-based triple therapy, and the available evidence is largely retrospective (an overview is presented in

Table 1). Gralla and Wiseman performed a retrospective analysis using U.S. registry data from primary kidney transplants performed during 2000–2008, comparing patients who received initial immunosuppression consisting of tacrolimus, MPA and prednisone with or without IL2RA induction (10). The 1-year acute rejection rate was 11.6% with IL2RA induction versus 13.0% with no induction. Although statistically significant, the clinical relevance of the difference is questionable, particularly because IL2RA induction did not improve graft or patient survival. In another retrospective study, based on a similar U.S. cohort, Willoughby et al compared outcomes between kidney transplant patients who received rATG (Thymoglobulin; Genzyme Corporation, Cambridge, MA), basiliximab or no induction, and attempted to improve comparability between groups by multivariable statistical adjustments and case matching (9). The 6-mo acute rejection rates were  $<15\%$  in all groups. In that study, rATG was associated with statistically superior outcomes regarding the composite triple end point of allograft rejection, graft failure or patient death compared with basiliximab, and both agents were superior to no induction. The size of the respective benefits, however, varied substantially between different statistical approaches, making it difficult to assess the true clinical benefit of one induction strategy versus another. By and large, 6-mo rejection rates were 13% without any induction, 11% with IL2RA and 9% with rATG, with no impact on graft or patient survival. More recently, Tanriover et al retrospectively analyzed U.S. registry data from patients who underwent living donor transplantation between 2000 and 2012 and who received tacrolimus, MPA and steroids (12). Propensity score analysis was used to minimize selection bias due to nonrandomized assignment of induction therapies. In this population, IL2RA induction was not associated with any improvement in outcomes compared with no induction (acute rejection at 1 year 11.7% vs. 12.4% [ $p = 0.55$ ]; similar graft survival at 5 years [ $p = 0.92$ ]). Data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) on renal transplant recipients between 1995 and 2005 also showed no reduction in rejection risk with IL2RA either in low-risk recipients or in tacrolimus-treated patients with intermediate immunological risk (RR 0.90, 95% CI 0.68–1.20;  $p = 0.48$ ) (11). Finally, two recent randomized controlled trials confirmed that low BPAR rates can be achieved with tacrolimus and MPA-based therapy without antibody induction (13,14). The very large OSAKA trial ( $n = 1251$ ) was designed to investigate the once-daily formulation of tacrolimus (13). In three of four study arms, patients received tacrolimus at different doses and formulations, together with MPA and steroids but without induction. BPAR rates were 10.3% (tacrolimus 0.2 mg/kg, twice a day), 12.7% (tacrolimus 0.2 mg/kg, once a day) and 16.1% (tacrolimus, 0.3 mg/kg once a day) at 24 weeks. Another randomized controlled trial ( $n = 212$ ) investigated induction with the recombinant LFA3/IgG1 fusion protein alefacept versus no induction in

patients receiving tacrolimus, MPA and steroids (14). The control arm showed a T cell-mediated BPAR rate of 7% and an antibody-mediated rejection rate of 2.8% at 6 mo. In summary, the available data suggest that for kidney transplant patients at standard immunological risk treated with tacrolimus, MPA and maintenance steroids, the benefit of IL2RA is very modest or nonexistent in terms of reducing acute rejection and does not confer a graft or patient survival advantage.

**Induction therapy in high-risk transplants**

The advantage of induction therapy appears to be more clear cut in high-risk kidney transplant recipients. Only two large randomized trials have compared IL2RA versus rATG induction specifically in this setting. Brennan et al recruited 278 patients at high risk of delayed graft function and/or acute rejection based on recipient characteristics such as HLA immunization or donor characteristics such as long cold ischemia time or advanced age (15). Maintenance therapy consisted of CsA, MPA and steroids. In contrast to standard-risk transplantation, in which acute rejection rates are similar with IL2RA and rATG

induction (4), Brennan and colleagues found rejection rates to be almost halved in high-risk patients given rATG versus IL2RA at 1 year (16% vs. 26%, p = 0.02) and at 5 years (15% vs. 27%, p = 0.03) (16). The severity of acute rejection episodes was also significantly lower with rATG. In another randomized trial, Noël et al enrolled 227 patients at high immunological risk (mean current panel reactive antibodies 35%), of whom almost three-quarters were receiving a second, third or fourth transplant (17). Maintenance therapy comprised tacrolimus, MPA and steroids. Again, both the incidence and severity of acute rejection were significantly lower with rATG versus IL2RA. The acute rejection rate at 1 year was 15% versus 27% (p = 0.016) (16), a difference that was maintained at 5-year follow-up (14% vs. 26%, p = 0.035) (18). The results of these two studies led to the 2009 KDIGO recommendation to use lymphocyte-depleting induction in patients at high immunological risk (4). Although both studies failed to show a difference in long-term graft- or patient survival benefit with rATG compared with IL2RA (16,18), lowering the incidence of acute rejection to this extent, given its inherent risks, costs and psychological

**Table 1:** The benefit of induction therapy in kidney transplantation with tacrolimus, mycophenolic acid, and steroid maintenance treatment

Study	Data source	Comparison	Acute rejection	Overall graft survival	Patient survival
Willoughby 2009 (9)	U.S. OPTN: first or second kidney transplants, 2001–2005, n = 19 137	IL2RA versus ATG versus no induction	AR <sup>1</sup> at 6 mo <sup>2</sup> : IL2RA: 11%; ATG: 9%; no induction: 13%	At 6 mo: IL2RA: 94%; ATG: 95%; no induction: 95%	At 6 mo: IL2RA: 98%; ATG: 97%; no induction: 98%
Gralla 2010 (10)	U.S. SRTR: first kidney transplants, 2000–2008, n = 28 686	IL2RA versus no induction	AR <sup>3</sup> at 1 year: IL2RA: 11.6%; no induction: 13.0% (p = 0.001)	At 3 years: IL2RA: 87.5%; no induction: 87.8% (p = 0.50)	At 3 years: IL2RA: 92.8%; no induction: 93.2%
Lim 2010 (11)	ANZDATA, 1995–2005: low risk: n = 1220; intermediate risk: n = 3204	IL2RA versus no induction	AR <sup>4</sup> at 6 mo: low risk: RR 1.00 (95% CI 0.71–1.43); intermediate risk: RR 0.74 (95% CI 0.63–0.88); intermediate risk on cyclosporine: RR 0.65 (95% CI 0.52–0.81); intermediate risk on tacrolimus: RR 0.90 (95% CI 0.68–1.20)	At 5 years; low risk: IL2RA: 84%; no induction: 86% (p = 0.40); intermediate risk: IL2RA: 81%; no induction: 81% (p = 0.94)	Low risk: RR 1.26 (95% CI 0.58–2.74); intermediate risk: RR 1.20 (95% CI 0.85–1.69)
Tanriover 2015 (12)	U.S. OPTN: live donor kidney transplants, 2000–2012, n = 25 996 <sup>5</sup>	IL2RA versus ATG versus no induction	AR <sup>6</sup> at 1 year: IL2RA: 11.7%; ATG: 9.6%; no induction: 12.4% (p < 0.001)	At 5 years: IL2RA: 88.3%; ATG: 90.4%; no induction: 87.6% (p = 0.07)	At 5 years: IL2RA: 91.5%; ATG: 92.5%; no induction: 89.1% (p < 0.001)

ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; AR, acute rejection; ATG, antithymocyte globulin; BPAR, biopsy-proven acute rejection; CI, confidence interval; IL2RA, IL-2 receptor antagonist; OPTN, Organ Procurement and Transplant Network; RR, relative risk; SRTR, Scientific Registry of Transplant Recipients.

<sup>1</sup>Defined as BPAR.

<sup>2</sup>Patients discharged with steroids. Approximation based on figure (no numbers provided in text).

<sup>3</sup>Defined as BPAR or “antirejection treatment given” or “clinically treated acute rejection.”

<sup>4</sup>Reported as AR (not otherwise specified).

<sup>5</sup>Patients on steroids at discharge, n = 25 996 (N = 36 153).

<sup>6</sup>Defined as BPAR or clinically treated rejection.

stress, can still be considered a valid argument for choosing rATG induction in high-risk transplants.

### **Induction therapy to support steroid-free immune suppression regimens**

Early steroid withdrawal or steroid avoidance has gained interest over the past decade following reports of its long-term safety and a possible reduction in posttransplant complications, although the latter remains unconfirmed (19,20). In a recent meta-analysis, early steroid avoidance (defined as <14 days of steroid therapy) was shown to be effective and safe in terms of graft and patient survival, with no increase in acute rejection, in patients receiving induction and tacrolimus-based maintenance therapy (19). The majority of patients in this meta-analysis who were randomized to early steroid avoidance received induction therapy (87%), most frequently with an IL2RA agent (IL2RA, 85%; rATG, 15%). Consequently, it was not possible to perform a meta-analysis of the effect of IL2RA versus rATG or no induction in this setting. The first question that needs to be addressed is whether there is a need for antibody induction to support steroid avoidance. No randomized trials have specifically addressed this, namely, by comparing induction versus no induction in two arms with an identical steroid-avoidance maintenance regimen. One large randomized trial included a steroid-free arm in which patients were given tacrolimus and MPA without antibody induction and a control arm in which patients received standard triple therapy with tacrolimus, MPA and steroids without induction (21,22). The cohort of 151 patients who received tacrolimus with MPA without induction and only a single perioperative dose of steroids displayed a very high rate of BPAR in the first 6 months after transplant (30.5%) compared with only 8.5% in the control arm (21). Although this did not seem to translate into poorer long-term outcomes—observational follow-up at 3 years showed similar graft survival (92.5% and 92.5%, respectively) and patient survival (96.4% and 97.0%, respectively) (22)—this high rate of BPAR concerns patients and medical staff. To avoid it, most centers still choose to use induction therapy in steroid avoidance strategies. This brings us to a second question: Which induction agent would be preferable? To our knowledge, no trial has randomized patients to IL2RA versus rATG with a regimen of early steroid avoidance. The best approximation comes from a large multicenter trial of early steroid withdrawal by Woodle et al, who included patients with either IL2RA or rATG induction, chosen at the investigator's discretion, with tacrolimus and MPA maintenance therapy (23). The investigators found slightly increased rates of BPAR after early steroid withdrawal in the study population overall (17.8% vs. 10.8% without steroid withdrawal,  $p = 0.04$ ), but the risk tended to be higher with IL2RA induction than with rATG (24.2% vs. 14.4% after early steroid withdrawal;  $p = 0.09$ ). A multivariate analysis combining the results of this trial with three other prospective trials by the

same investigators also showed a tendency toward a lower risk of acute rejection when early steroid avoidance was accompanied by rATG induction compared with no rATG (IL2RA or no induction; odds ratio 0.61, 95% CI 0.30–1.27) (24). Finally, a recent large retrospective analysis based on national U.S. registry data from kidney transplant recipients discharged on steroid-free maintenance immunosuppression showed higher adjusted graft survival with rATG than IL2RA induction (hazard ratio 1.19, 95% CI 1.01–1.39) (25). Although a robust comparison of no induction, IL2RA and rATG is lacking, current data suggest that early steroid withdrawal is safe in patients receiving induction therapy with a maintenance regimen that includes a calcineurin inhibitor and MPA and that there is a clear trend toward higher effectiveness with rATG compared with IL2RA induction.

### **Conclusions**

The use of induction therapy is now routine after kidney transplantation, but much uncertainty remains regarding its benefits versus potential risks when used as a part of contemporary posttransplant management. In previous eras, induction with IL2RA agents or ATG led to a substantial reduction in early acute rejection; however, with widespread use of tacrolimus and MPA combination therapy conferring a lower baseline acute rejection risk, the incremental benefit of induction therapy has become questionable in standard-risk recipients. The available data, mostly from retrospective registry analyses, indicate that in standard-risk recipients on tacrolimus and MPA-based triple maintenance therapy, the addition of induction therapy with IL2RA or ATG may achieve, at best, an absolute risk reduction for acute rejection of  $\approx 1$ –4% but with no improvement in graft or patient survival (9–14). This minor benefit should be balanced against the expense and the risks of induction therapy, including a possible increase in infectious and malignant complications. The situation is different for kidney transplant patients at high immunological risk, for whom induction therapy—particularly rATG—lowers the risk of acute rejection much more substantially. Using rATG, the RR of acute rejection is almost 50% lower than with IL2RA in patients with high immunological risk. Although rATG has not been shown to improve graft survival compared with IL2RA, lowering the incidence of acute rejection to this extent could still be considered a valid argument for its use in this particular population. Moreover, in early steroid avoidance, which could be considered to be another high-risk situation, the role of induction therapy seems to be more important, and again, there is a clear trend toward higher effectiveness of ATG compared with IL2RA induction. Concerns about the safety of rATG, which has historically been associated with a higher risk of infections and malignancy compared with IL2RA induction (4,26–29), are declining based on recent studies in which rATG dosing was lower than in the past (30–34). Nevertheless, high-quality evidence to

accurately gauge the long-term side effects of induction therapy is lacking.

In conclusion, we feel that the role of IL2RA in contemporary kidney transplantation has become questionable because it may no longer be beneficial in standard-risk transplantation and may be inferior to rATG in high-risk settings. We should be careful, however, not to draw overly strong conclusions based mainly on retrospective registry data, which have an inherent risk of selection bias and typically lack detailed information on the immunosuppressive treatment that was given. Registry databases, for example, do not capture the reason why one induction agent was chosen over another, and they do not provide data on the timing and dosage of either induction agents or maintenance immunosuppressants. Ideally, the true impact of induction therapy in today's standard-risk transplant recipients should be retested in a randomized controlled study with contemporary maintenance therapy; however, it is very unlikely that such a trial will ever be performed, given the large number of patients required to reach adequate power with such small expected differences in outcome. We also acknowledge that detailed information on possible differences in long-term GFR and infectious or malignancy risks is lacking. Nevertheless, based on graft and patient survival rates, there are no clear indications that omitting induction therapy in standard-risk kidney transplant patients receiving tacrolimus, MPA and steroids would lead to inferior long-term outcomes. Updated evidence-based guidelines are necessary to support clinicians in deciding whether and what induction therapy is required for their transplant recipients today.

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