Induction Therapy in Renal Transplantation: Why? What Agent? What Dose? We May Never Know

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Induction therapy, defined simply as the short-term use of an immunosuppressive agent, has become commonplace in kidney transplantation. Historically, induction therapy had been considered necessary to prevent acute rejection and typically included the use of high doses of corticosteroids and/or more specific T cell–directed therapy. Such agents include the polyclonal rabbit antithymocyte globulin (rATG; Thymoglobulin, first available in Europe in 1984 and the United States in 1999), the murine anti-CD3 mAb Muromonab-CD3 (OKT3; the first mAb approved for human use in 1986, but it is no longer in production), the humanized anti-CD52 mAb alemtuzumab (Campath-1H; gradually introduced in kidney transplantation in the 1990s and into the last decade), and finally, mAbs directed against the IL-2 receptor (IL-2ra; including basiliximab, which was approved for kidney transplantation in 1998, and daclizumab, which was approved in 1997 but subsequently withdrawn in 2009). In general, rATG and alemtuzumab are distinguished mechanistically from basiliximab in that the former are T cell–depleting agents with a prolonged recovery of T cell counts over months, whereas the latter is a nondepleting agent that acts to inhibit T cell proliferation in response to IL-2. Another important distinguishing feature is that neither rATG nor alemtuzumab is Food and Drug Administration (FDA) approved as an induction agent in the United States.

As one can surmise by the timeline of introduction of these agents, all induction agents gained traction as vital therapy for antirejection prophylaxis during prior eras of maintenance immunosuppression, using agents that may be considered less potent than the maintenance immunosuppression that we currently use. In the United States, the rapid succession of approval of tacrolimus (TAC) in 1994, mycophenolate (MPA) mofetil in 1995, and sirolimus in 1999 led to many combinations of agents that were proven to be advantageous over older agents, such as cyclosporin or azathioprine, in the prevention of acute rejection, but they were studied in parallel and not head to head. This led to use of various combinations of agents over the subsequent decade without stringent clinical trial data supporting the practice. The evolution of induction agent use over the past 10–15 years was concurrent with evolving maintenance immunosuppression use (including the increased application of early corticosteroid withdrawal) (1) (Figure 1). Highlighting this point, there has never been a randomized, controlled, double-blind clinical trial comparing the combination of TAC and MPA with any other maintenance combination, and there has not been a randomized, controlled, double-blind clinical trial comparing induction agents. Ultimately, the transplant community evolved practice patterns that are summarized and supported by the 2009 Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines, which states that induction therapy should be used (level 1A recommendations; "we recommend ... based on high quality evidence" [2]), despite the lack of studies as described above and despite the lack of any 1A recommendations for any specific agent (2).

With this in mind, the study by Tanriover *et al.* (3) published in this issue of *CJASN* addresses the lack of data supporting the use of induction therapy in a lower-risk patient population (first transplants in recipients of living donor kidney transplants) who received a standard maintenance immunosuppression regimen of TAC and MPA with or without maintenance corticosteroids (PRED). The important findings of this large retrospective analysis of recipients of kidney transplants in a modern era of immunosuppression (2000–2012) include the following findings (3). (*1*) There was no benefit from use of IL-2ra induction versus no induction in patients maintained on TAC/MPA/PRED with respect to acute rejection or graft survival (3). (*2*) rATG use was associated with 22% (combined with steroids) and 27% (in the setting of steroid withdrawal) reductions in the risk of acute rejection compared with IL-2ra, with no effect on graft survival (3). (*3*) In the setting of steroid withdrawal, alemtuzumab was associated with a 47% reduction in risk of acute rejection compared with IL-2ra and a 27% increased risk of graft loss (3).

The primary strengths of this study include the standardization of baseline immunosuppression, and, more importantly, the use of propensity score methodology to address the selection bias that is almost certainly present as transplant programs determine the appropriate need/degree of induction therapy for their programs or an individual patient (3). This statistical approach has not been previously used when addressing this topic and is superior to previous meta-analyses and retrospective analyses that have attempted to compare induction agents (4,5). The weaknesses of this

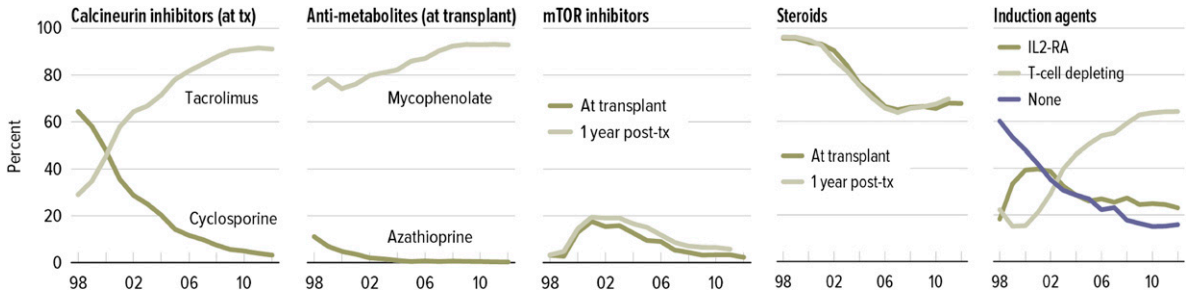

Figure 1. | **Evolution of maintenance and induction immunosuppression use 1998–2012 (17).** IL2-RA, IL-2 receptor; tx, transplant.

study and all other retrospective studies examining the effect of induction include (*1*) the lack of information regarding the intensity of maintenance immunosuppression (for example, higher TAC trough levels may have been used in the absence of induction), (*2*) the uncertainty regarding the longer-term effect of induction on graft survival (the mean time of follow-up was approximately 4 years, perhaps too short to determine long-term safety of depleting antibody strategies [6,7]), (*3*) the lack of clarity in determining the influence of rejection on graft outcomes (the type and severity of rejection and the response to therapy, important factors in assigning prognosis, may be different if rejection occurred after induction with one agent versus another or in the absence of induction [8]), and finally, (*4*) the lack of information regarding longer-term markers of immunologic injury, such as the rates of *de novo* donor-specific antibody formation in both those with or without induction and those with rejection under various induction strategies (3). Although rejection is a risk factor for future donor-specific antibody formation, is not known if induction or a specific induction agent alters this predilection (9).

Given these weaknesses, could this study actually change clinical practice patterns? It should be recognized that these data may be as good as it gets and that we will never see a randomized, controlled trial comparing IL-2ra with no induction or rATG in the context of corticosteroid maintenance or a randomized, controlled, double-blind study comparing IL-2ra with either rATG or alemtuzumab in the context of steroid withdrawal. Because the incidence of rejection is approaching 10% in low-risk patients, the sample size required of these studies to show a statistically and clinically meaningful difference is too great (and thus, too expensive). From the sponsor/manufacturer's point of view, such studies are too risky given the current widespread use of induction. Given the lack of data regarding baseline immunosuppression and other weaknesses noted above, transplant centers likely will continue their own individualized protocols, unless constrained by the additional cost of induction. Particularly in the setting of steroid maintenance, the costs and potential side effects of induction therapy may not warrant induction with either IL-2ra or rATG when one considers that even a 25% reduction in risk of acute rejection from 15% to 12% or from 12% to 9% requires treatment of 33 patients to avoid one episode of acute rejection, with no discernable advantage on long-term graft survival.

Another issue not addressed by this study is the total exposure of rATG and alemtuzumab. Given the cost of rATG and relatively modest effect on efficacy, it is not surprising that transplant centers have continually reduced the overall dosing over time (from 10 to 3 mg/kg in low-risk patients [10–12]) and attempted to streamline dosing (from 10 days to a continuous 24-hour period in one center [13]) to reduce cost without reducing its effect on rejection rates. Could it be that even less rATG is needed (closer to zero)? Again, this will never be studied in a multicenter, prospective fashion, and therefore, single-center experiences will be all that guides us in this regard. It is also not surprising that alemtuzumab was introduced to kidney transplantation given its significant cost advantages and simplified dosing (14). However, with the withdrawal of alemtuzumab from the United States market for kidney transplant, only institutional review board–approved use of alemtuzumab will occur in the future, and a multicenter study of alemtuzumab versus rATG in the setting of TAC/MPA/±PRED is not likely to be a high priority.

Could this study change clinical practice guidelines or regulatory approval? Data accumulating subsequent to KDIGO guidelines certainly support the facts that IL-2ra may not be required for low-risk patients on TAC/MPA/PRED (15) and that depleting antibody induction reduces the risk of acute rejection in the setting of steroid withdrawal (14,16). Perhaps future guideline iterations will downgrade the recommendation for induction in low-risk groups and upgrade their recommendations for depleting antibodies in high-risk groups and with corticosteroid withdrawal. From a regulatory standpoint, the FDA has been inflexible to date with respect to granting approval for rATG in the absence of a placebo-controlled trial or a double-blind comparison with another FDA-approved agent (*e.g.*, IL-2ra), but the precedent for approval of TAC combined with MPA in 2009 set the stage for the possibility of approval to occur in the absence of such trials. This would permit future induction agents to be developed and tested against the current standard of care.

Ultimately, Tanriover *et al.* (3) have brought attention to the holes in our current knowledge of the appropriate need, type, and dose of immunosuppression in low-risk patient populations. To the credit of Tanriover *et al.* (3) and the field's misfortune, these holes are unlikely to be addressed with greater rigor in study design than they were in this work.

Disclosures

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References

1. Matas AJ, Smith JM, Skeans MA, Thompson B, Gustafson SK, Stewart DE, Cherikh WS, Wainright JL, Boyle G, Snyder JJ, Israni AK, Kasiske BL: OPTN/SRTR 2013 Annual Data Report: kidney. *Am J Transplant* 15[Suppl 2]: 1–34, 2015
2. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group: KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant* 9[Suppl 3]: S1–S155, 2009
3. Tanriover B, Zhang S, MacConmara M, Gao A, Sandikci B, Ayvaci MUS, Mete M, Tsapepas D, Rajora N, Mohan P, Lakhia R, Lu CY, Vazquez M: Induction therapies in live donor kidney transplantation on tacrolimus and mycophenolate with or without steroid maintenance. *Clin J Am Soc Nephrol* 10: 1041–1049, 2015
4. Gralla J, Wiseman AC: The impact of IL2ra induction therapy in kidney transplantation using tacrolimus- and mycophenolate-based immunosuppression. *Transplantation* 90: 639–644, 2010
5. Webster AC, Ruster LP, McGee R, Matheson SL, Higgins GY, Willis NS, Chapman JR, Craig JC: Interleukin 2 receptor antagonists for kidney transplant recipients. *Cochrane Database Syst Rev* 1: CD003897, 2010
6. Hall EC, Engels EA, Pfeiffer RM, Segev DL: Association of antibody induction immunosuppression with cancer after kidney transplantation [published online ahead of print October 21, 2014]. *Transplantation*
7. Ducloux D, Courivaud C, Bamoulid J, Crepin T, Chalopin JM, Tiberghien P, Saas P: Polyclonal antithymocyte globulin and cardiovascular disease in kidney transplant recipients. *J Am Soc Nephrol* 25: 1349–1356, 2014
8. Wu K, Budde K, Lu H, Schmidt D, Liefeldt L, Glander P, Neumayer HH, Rudolph B: The severity of acute cellular rejection defined by Banff classification is associated with kidney allograft outcomes. *Transplantation* 97: 1146–1154, 2014
9. Wiebe C, Nickerson P: Posttransplant monitoring of de novo human leukocyte antigen donor-specific antibodies in kidney transplantation. *Curr Opin Organ Transplant* 18: 470–477, 2013
10. Hardinger KL, Schnitzler MA, Koch MJ, Labile E, Stirnemann PM, Miller B, Enkvetchakul D, Brennan DC: Thymoglobulin induction is safe and effective in live-donor renal transplantation: A single center experience. *Transplantation* 81: 1285–1289, 2006
11. Klem P, Cooper JE, Weiss AS, Gralla J, Owen P, Chan L, Wiseman AC: Reduced dose rabbit anti-thymocyte globulin induction for prevention of acute rejection in high-risk kidney transplant recipients. *Transplantation* 88: 891–896, 2009
12. Peddi VR, Bryant M, Roy-Chaudhury P, Woodle ES, First MR: Safety, efficacy, and cost analysis of thymoglobulin induction therapy with intermittent dosing based on CD3+ lymphocyte counts in kidney and kidney-pancreas transplant recipients. *Transplantation* 73: 1514–1518, 2002
13. Stevens RB, Foster KW, Miles CD, Lane JT, Kalil AC, Florescu DF, Sandoz JP, Rigley TH, Nielsen KJ, Skorupa JY, Kellogg AM, Malik T, Wrenshall LE: A randomized 2×2 factorial trial, part 1: Single-dose rabbit antithymocyte globulin induction may improve renal transplantation outcomes. *Transplantation* 99: 197–209, 2015
14. Hanaway MJ, Woodle ES, Mulgaonkar S, Peddi VR, Kaufman DB, First MR, Croy R, Holman J; INTAC Study Group: Alemtuzumab induction in renal transplantation. *N Engl J Med* 364: 1909–1919, 2011
15. Gralla J, Le CN, Cooper JE, Wiseman AC: The risk of acute rejection and the influence of induction agents in lower-risk African American kidney transplant recipients receiving modern immunosuppression. *Clin Transplant* 28: 292–298, 2014
16. Woodle ES, First MR, Pirsch J, Shihab F, Gaber AO, Van Veldhuisen P; Astellas Corticosteroid Withdrawal Study Group: A prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 day) corticosteroid cessation versus long-term, low-dose corticosteroid therapy. *Ann Surg* 248: 564–577, 2008
17. OPTN/SRTR: OPTN/SRTR 2012 Annual Data Report. Available at: http://srtr.transplant.hrsa.gov/annual_reports/2012/pdf/01_kidney_13.pdf. Accessed April 6, 2015

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See related article, "Induction Therapies in Live Donor Kidney Transplantation on Tacrolimus and Mycophenolate With or Without Steroid Maintenance," on pages 1041–1049.