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INVITED COMMENTARY

Where do we stand in 2020 regarding induction therapy after kidney transplantation?

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Introduction

Human leukocyte antigen (HLA) sensitization remains a huge barrier to transplantation, especially in the setting of kidney transplantation and particularly for women that have had pregnancies and those that are repeat kidney-transplant candidates. Indeed, patients that are HLA sensitized are more prone to develop post-transplant acute rejection as are those that are sensitized at pretransplant against the donor, that is, they have preformed donor-specific alloantibodies (DSAs). These patients have a greater risk of hyperacute rejection and antibody-mediated rejection (ABMR; acute or chronic). The presence of pretransplant cytotoxic DSAs precludes transplantation unless the patient undergoes pretransplant desensitization [1].

Panel-reactive antibodies are widely regarded as an important immunological risk factor for kidney rejection and allograft loss. The broadness of sensitization against HLA is most appropriately measured by obtaining the value of "calculated population-reactive antibodies" (cPRA). cPRA is based on unacceptable HLA antigens to which the patient has been sensitized and, if present in a donor, represents an unacceptable risk for the candidate [2].

The presence of PRA is significantly associated with an increased risk of acute rejection [3,4], and graft failure [5]. In a recent study, Wehmeier *et al.* [6] reported that the strongest independent predictor for ABMR and (death-censored) graft survival was pretransplantation DSAs; conversely, cPRA was not predictive for ABMR, T-cell mediated rejection or (death-censored) graft survival.

Is induction therapy worth it?

Recently, Hill *et al.* (Cochrane Library) evaluated, through a meta-analysis, the relative and absolute effects of different lymphocyte-depleting antibody preparations when used as induction therapy for kidney transplant recipients [mostly from deceased donors (DD) and with low-immunological risk]. Overall, antithymocyte globulins (r-ATG) and alemtuzumab decreased acute rejection, but at the cost of increased cytomegalovirus

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(CMV) disease. Also, patients' outcomes (reduced death or lower toxicity) did not appear to be improved [7]. However, Gharibi *et al.* performed a study to estimate the cumulative costs, graft survival and the incremental cost-effectiveness ratio (ICER—cost per additional year of graft survival) within 3 years of transplantation of induction therapy. They included 19 450 DD kidney transplant recipients with Medicare as the primary payer between 2000 and 2008. They found that antibody-based induction seemed to offer substantial advantages in both cost and outcomes compared with no induction. Overall, induction by depletion (preferably r-ATG) appeared to offer the greatest benefits [8].

Induction therapy in live kidney transplant recipients

Based on data from the Organ Procurement and Transplantation Network (OPTN) registry, between 1998 and 2008, 48 756 patients received a live-kidney transplant. They received either no induction therapy or received an induction therapy of r-ATG or IL-2RA. Most patients had PRA of <10%. Although antibody induction was associated with a decreased risk of acute rejection between 1998 and 2002, it was not associated with a decreased risk of acute rejection between 2003 and 2008, nor was it associated with a difference in graft survival within either time span [9].

Likewise, based on data from the OPTN registry between 2000 and 2012, 36 153 live kidney transplant recipients received tacrolimus (TAC)/mycophenolic acid (MPA) at discharge, Tanriover *et al.* reported that, compared to no induction therapy, induction with IL2-RA, r-ATG and alemtuzumab was not associated with better outcomes in steroid-maintained patients, that is, acute-rejection rate, overall allograft failure risk. However, patients with early steroid withdrawal, and those that were induced with r-ATG and alemtuzumab (vs. no induction or IL2-RA induction) had a significantly lower acute-rejection rate, but similar allograft-survival rates [10].

These results do not necessarily favor induction therapy in low-immunological risk live kidney transplant recipients.

Induction therapy in deceased-donor, nonbroadly sensitized kidney transplant recipients

Recently, Sureshkumar *et al.* evaluated the benefit of induction therapy on the outcomes of low-immunological risk DD kidney transplant recipients (first transplant, PRA <20%, HLA mismatches ≤3) using a mate-kidney model. By using the OPTN database, three groups were generated with each group containing recipients with mate-kidneys from the same donor and only differing according to the induction therapy they received: group 1: no induction versus IL2-RA induction; group 2: no induction vs. depleting antibody induction; group 3: IL2RA vs. depleting antibody induction. Adjusted 5-year graft-survival rates were similar between mate-kidney recipients in all three groups. However, the adjusted risk of patient death was significantly lower in patients that had lymphocyte-depleting antibody induction (group 2; HR 0.48, 95% CI 0.26–0.88, $P = 0.02$) and trended lower in patients induced with IL2RA (group 1; HR 0.32, 95% CI 0.10–1.01, $P = 0.05$). Thus, perioperative antibody induction was associated with a lower risk of patient death in low-immunologic risk DD kidney transplant recipients [11].

Koyawala *et al.*, using OPTN data to compare a broad range of outcomes according to the induction strategy, generated 1:1 pairs of alemtuzumab-rATG (5330 pairs) and basiliximab-rATG (9378 pairs) kidney transplant recipients (mostly from deceased donors with PRA <80% and that had received a transplant between 2003 and 2008). Primary outcomes were death or allograft failure; secondary outcomes included death or sepsis, death or lymphoma, death or melanoma, and healthcare resource utilization within 1 year. Compared to r-ATG recipients, those receiving alemtuzumab had a higher risk of death [hazard ratio (HR), 1.14; 95% CI, 1.03–1.26; $P < 0.01$] and death or allograft failure (HR, 1.18; 95% CI, 1.09–1.28; $P < 0.001$). Compared to r-ATG recipients, those receiving basiliximab had a higher risk of death (HR, 1.08; 95% CI, 1.01–1.16; $P = 0.03$) and death or lymphoma (HR, 1.12; 95% CI, 1.01–1.23; $P = 0.03$), although these differences were not confirmed in the subgroup analysis. One-year resource utilization was slightly lower among alemtuzumab recipients than among r-ATG recipients but did not differ between basiliximab and r-ATG recipients. The authors concluded that, compared to alemtuzumab and basiliximab, r-ATG was associated with a lower risk of adverse outcomes, including mortality [12].

Thomusch *et al.* conducted an open-label, multicenter, randomized controlled trial that included 615 low-immunological risk kidney transplant recipients (no PRA in more than 80% of patients) and most were recipients from deceased donors. The patients were randomly assigned in a 1:1:1 ratio to receive either basiliximab as the induction therapy with low-dose

tacrolimus, mycophenolate mofetil, and steroid maintenance (arm A), or rapid corticosteroid withdrawal on day 8 (arm B), or rapid corticosteroid withdrawal on day 8 after rabbit ATG (arm C). At 1-year post-transplantation, biopsy-proven acute rejection (BPAR) and patient- and graft-survival rates were similar across the three groups. However, *de novo* post-transplant diabetes (PTDM) was significantly reduced in patients that had undergone rapid steroid withdrawal. Infections and the incidence of post-transplantation malignancies did not differ between the study arms [13].

Masset *et al.* conducted a study that included 383 low-immunological risk (PRA = 0%) elderly (>65 years) kidney transplant recipients receiving TAC/MPA/+/− steroids. They found that, at 3 years post-transplantation, patient- and graft-survival rates were similar. PTDM was significantly higher in the basiliximab group (23% vs. 15%, $P = 0.04$) due to higher trough levels of TAC in month 3 (9.48 vs. 7.30 ng/ml, $P = 0.023$). They concluded that these elderly recipients did not have worse outcomes with ATG compared to those receiving basiliximab and, thus, this could permit lower trough levels of tacrolimus and so reduce the occurrence of PTDM [14].

Popat *et al.* evaluated induction therapies (basiliximab vs. r-ATG) given to 45 kidney-transplant patients whose recipients were organ donors after cardiac death (DCD). They found that patient- and graft-survival rates were similar in both groups. However, there was a significantly lower rate of delayed graft function, BPAR and infection that required readmission in r-ATG group. A cost analysis was performed that included all immunosuppression-related costs; it showed remarkable savings in the ATG-induced group [15].

Induction therapy in kidney transplant recipients with preformed donor-specific anti-HLA antibodies

There are some data regarding induction therapy in the setting of preformed DSAs. Recently, Uffing *et al.* performed a retrospective analysis in 179 DD kidney transplant recipients with solely DSA class II before transplant and patients without DSA and compared graft survival, rejection, and clinical outcomes. Patient survival was also compared with matched controls on the waiting list. After a mean follow-up of 5.5 years, there was no significant difference in death-censored graft survival between transplanted patients without DSA and those with preformed DSA class II (adjusted HR 1.10; 95% confidence interval, 0.41–2.97), although the incidence of rejection was higher in recipients with DSA class II (adjusted HR 5.84; 95% confidence interval, 2.58–13.23; $P < 0.001$). Serum creatinine levels at 1, 3 and 5 years post-transplant did not differ between groups. No predictors of rejection were found, although patients who received basiliximab induction therapy had higher incidence of rejection (100%) compared with those who received antithymocyte globulin (52%) [16]. In a review paper, Pascual *et al.* demonstrated that in kidney-transplant patients with low-strength preformed DSAs, noncomparative data have shown a low incidence of ABMR and graft survival using r-ATG even without desensitization procedures. For high strengths of preformed DSAs, r-ATG induction with more aggressive desensitization appears effective, with mixed results concerning the addition of B-cell specific agents. Observational data in moderately sensitized kidney-transplant patients suggest that the incidence of *de novo* DSA and ABMR is significantly lower with r-ATG versus basiliximab. Overall, r-ATG appears to inhibit DSA production, with a potential role in reducing the risk of ABMR in kidney-transplant patients with high-strength preformed DSA or lowering *de novo* DSA in moderately sensitized patients [17].

Induction therapy in nonbroadly sensitized DD kidney transplant recipients

Recently, Kamar *et al.* conducted a multicenter, randomized controlled trial that included 59 HLA sensitized (cPRA >50%) DD kidney transplant recipients without any DSAs (as detected by Luminex®). Immunosuppression relied on steroids, TAC and MPA, with an induction therapy of either anti-T lymphocyte globulin (ATLG; Grafalon®; Neovii Biotech, Lexington, MA, USA) or basiliximab. At 1-year post-transplantation, patient survival, rejection-free survival and graft loss were similar across the two groups [18].

In this issue of *Transplant International*, Santos *et al.* [19] studied the outcomes after induction antibody therapy (r-ATG, alemtuzumab and IL2-RA) in adult DD kidney transplant recipients that were nonbroadly sensitized (cPRA < 80%). In order to achieve this, they studied the data from 55,593 kidney transplant recipients, recorded in the Scientific Registry of Transplant Recipients (SRTR), and that had received a transplant between 2007 and 2017. The patients' maintenance immunosuppression relied on TAC/MPA+/− steroids, and the induction therapy was one of the following: r-ATG, alemtuzumab or IL2-RA [19]. Immunological risk stratification, based on cPRA, was

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either <10% or 10–79%. Primary outcomes were overall graft survival, death-censored graft survival and patient survival at 5 years after kidney transplantation. A propensity score (PS) was used to control for confounding bias in ascertaining the different induction therapies. PS is the multinomial logistic regression-derived conditional probability of a kidney-transplant recipient being given an induction therapy based on a pre-existing or predetermined potentially confounding variable. The 5-year patient survival was similar across the three induction regimens, regardless of cPRA. The 5-year overall graft survival was similar across the three groups in the 10–79% cPRA cohort. Conversely, in the <10% cPRA cohort, the differences between the induction subgroups were very small, ranging between 0.64% and 1.32%, and the only significant almost negligible difference was between r-ATG vs. alemtuzumab (diff. = 0.64%, 95% CI 0.20–1.08; $P_{adj} = 0.012$). With regards to 5-year death-censored graft survival (DCGS) in the <10% cPRA cohort, alemtuzumab had a minimally lower DCGS probability than ATG or IL-2RA (diff. = −1.4%, 95% CI −0.70 to − 0.21; $P_{adj} < 0.0001$ and diff. = −1.3%, 95% CI −1.96 to −0.64; $P_{adj} < 0.0001$, respectively). DCGL risks were similar between the ATG and IL-2RA groups. In the 10–79% cPRA cohort, alemtuzumab had a minimally lower DCGS probability than r-ATG or IL-2RA (diff. = −1.66%, 95% CI −0.35 to −0.297; $P_{adj} = 0.033$ and diff. = −2.81%, 95% CI −4.42 to −1.2; $P_{adj} = 0.003$, respectively). r-ATG and IL-2RA had similar DCGL risks. Re-hospitalization in the first post-transplant year was consistently lower for the IL2-RA groups compared with the r-ATG and alemtuzumab groups, regardless of cPRA. In both the <10% cPRA and 10–79%cPRA cohorts, there were significantly higher rates of BPAR in IL2-RA-treated patients, that is, ~11%, compared to those treated with r-ATG or alemtuzumab (i.e., <8%). In both cPRA cohorts, *de novo* malignancy rates were similar across the three induction groups. However, this study has major limitations: that is, it uses registry data where they may be underreporting of events, such as BPAR, *de novo* malignancies. In addition, maintenance immunosuppression relied only on discharge treatment and there was no information on tacrolimus and MPA exposure within the 5-year post-transplantation data.

Because we assume that induction therapy is worthwhile, although not based on robust long-term data, (i.e., in the setting of large randomized controlled trials), the literature, mostly based on registry data and meta-analyses, does favor induction therapy, and particularly when based on r-ATG.

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Conflicts of interest

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