INVITED COMMENTARY

Utility or futility of Interleukin 2 receptor antagonist (IL2RA) induction in kidney transplants—the devil is in the detail

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Induction therapy is used routinely in kidney transplantation and has been recommended by the 2009 Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline as a level 1A recommendation [1]. However, which agent should be used for induction and in which patient remains a matter of debate. Induction agents currently in use include depleting (usually, polyclonal anti-thymocyte globulin derived from rabbit—rATG) or nondepleting (Interleukin 2 receptor antagonists—IL2RA) agents.

Clinical trials evaluating IL2RA with placebo and IL2RA with ATG were reviewed in a meta-analysis by Webster *et al.* [2] for Cochrane database. Their study found that IL2RA reduced graft loss by 25% at 6 months and 1 year and reduced biopsy proven acute rejection (BPAR) at 1 year by 28%. IL2RA compared to ATG was associated with 30% higher risk for BPAR but with similar graft survival and lower risk of malignancy and CMV disease. Recipients in these studies were predominantly low risk. Randomized studies comparing ATG with IL2RA in high-risk transplant recipients [3–6] showed that rejection rates were significantly lower with ATG at 1 year (16% vs. 26% [3], 15% vs. 27% [5]) and 5 years [4,6] and the severity of rejection (need for antibody treatment) was also lower. Based on these studies KDIGO [1] recommended IL2RA as first-line induction agent and lymphocyte-depleting agents for high immunological risk transplants. This should have settled the debate on which induction to use and when.

However, the randomized studies used in the Cochrane meta-analysis predominantly had maintenance immunosuppression of cyclosporine and azathioprine and high rejection rates of ~35–50%. With switch in maintenance immunosuppression currently to Tacrolimus and Mycophenolate Mofetil rejection rates decreased significantly and is currently ~10%. The utility of IL2RA as an induction agent with current maintenance immunosuppression protocols has been questioned [7–9]. No randomized clinical trial has compared IL2RA with placebo with tacrolimus and mycophenolate maintenance

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immunosuppression and such a study is unlikely to be conducted. To answer this question multiple investigators have used retrospective data analysis to compare IL2RA with no induction. Gralla and Wiseman [10] evaluated US registry data from 2000 to 2008 and found lower rejection rate of 11.6% vs. 13% at 1 year, after multivariable adjustment IL2RA was associated with a 10% risk reduction. Tanriover *et al.* [11] evaluated the US registry data from 2000 to 2012 for living donor transplants and compared IL2RA with no induction in those with triple immunosuppression (tacrolimus, mycophenolate, and steroids). Propensity score was used to reduce selection bias and no benefit of IL2RA was found for acute rejection or graft survival. IL2RA was also compared with ATG or alemtuzumab in steroid avoidance protocols and ATG decreased rejection by 27% with no difference in graft survival while alemtuzumab reduced rejection by 47% but had lower graft survival. Opelz *et al.* [12] analyzing CTS data also showed no beneficial effect of antibody induction in normal risk kidney transplants. Lim *et al.* [13] using ANZDAT data base also concluded that IL_2RA induction does not reduce rejection risk in low immunological risk renal transplant recipients.

Hence, at present ATG should be used as induction for high immunological risk individuals or those in a steroid avoidance protocol. For those with low risk, no induction or IL2RA may be considered based on cost, baseline rejection risk in the transplant program or patient preference.

In this background comes the study from Goumard *et al.* [14] published in this issue. The study tries to assess patients at intermediate risk (sensitized patients with anti-HLA antibodies but no donor specific antibodies DSA) and assess if IL2RA compared to ATG might provide similar efficacy (rejection and graft survival) and better safety (infection and malignancy). The study is a retrospective analysis of 218 sensitized recipients with no DSA transplanted between 2007 and 2016 at a single center with Basiliximab (60) or rATG (158). Primary outcome is BPAR and a composite outcome of BPAR, graft loss and death. Basiliximab was associated with a higher risk of BPAR (HR 3.6) and composite endpoint (HR 1.8) and similar infection and malignancy. The results did not alter with multiple adjustments.

The limitations of this kind of analysis are the vastly different kind of recipients who receive the different induction agent (selection bias) as is seen in this study. Higher risk patients were given ATG—higher PRA (64% vs. 24%), more re-transplants (46% vs. 13%) and less living donors (1.9 vs. 13.3%), and longer cold ischemia. Basiliximab group did have higher Class II mismatches (2.2 vs. 1.7). It is also important to note that because of lymphopenia, ATG patients received less MMF dose at 3, 6, and 12 months. Despite these higher risk factors, rejection rates were lower in those who received ATG compared to basiliximab suggesting that even these intermediate risk transplants would benefit from ATG over basiliximab.

Important details of the transplant protocol to keep in mind and which may limit its generalizability are:

1. Protocol biopsy at 3 months (~80% patients in each group had a biopsy during the study). In total, ~50% of the BPAR were discovered on protocol biopsy.
2. Steroid withdrawal within 1 year (in the absence of clinical or subclinical rejection, absence of denovo DSA, PRA, and risk of recurrence). This makes the group a late steroid withdrawal and may explain the later rejections and outcomes may have been different if steroid had been continued, especially as the basiliximab group with the lower PRA may have been more likely to have their steroid withdrawn. The authors do mention that overall steroid duration and doses were similar.
3. The study had a DSA monitoring, CMV and BK monitoring protocol, and adjustment of immunosuppression based on viremia.
4. Significant fraction of patients (8%) with basiliximab started with mTOR and then additional ~5% in each group switched to it by 3 months. This could also be a possible cause for increased risk of rejection as mTOR at transplant or switching to mTOR is a known risk factor for rejection. The authors have done additional analysis to limit the analysis to only those who had a tacrolimus, mycophenolate, and steroid regimen.

This study adds to the growing literature of the benefit of ATG over IL2RA in reducing rejection in intermediate or high immunological risk. The utility or futility of IL2RA in low immunological risk transplant (which is the majority of transplants) remains unanswered.

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