

## Antibody induction therapy in adult kidney transplantation: A controversy continues

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### Abstract

Antibody induction therapy is frequently used as an adjunct to the maintenance immunosuppression in adult kidney transplant recipients. Published data support antibody induction in patients with immunologic risk to reduce the incidence of acute rejection (AR) and graft loss from rejection. However, the choice of antibody remains controversial as the clinical studies were carried out on patients of different immunologic risk and in the context of varying maintenance regimens. Antibody selection should be guided by a comprehensive assessment of immunologic risk, patient comorbidities, financial burden as well as the maintenance immunosuppressives. Lymphocyte-depleting antibody (thymoglobulin, ATGAM or alemtuzumab) is usually recommended for those with high risk of rejection, although it increases the risk of infection and malignancy. For low risk patients, interleukin-2 receptor antibody (basiliximab or daclizumab) reduces the incidence of AR without much adverse effects, making its balance favorable in most

patients. It should also be used in the high risk patients with other medical comorbidities that preclude usage of lymphocyte-depleting antibody safely. There are many patients with very low risk, who may be induced with intravenous steroids without any antibody, as long as combined potent immunosuppressives are kept as maintenance. In these patients, benefits with antibody induction may be too small to outweigh its adverse effects and financial cost. Rituximab can be used in desensitization protocols for ABO and/or HLA incompatible transplants. There are emerging data suggesting that alemtuzumab induction be more successful than other antibody for promoting less intensive maintenance protocols, such as steroid withdrawal, tacrolimus monotherapy or lower doses of tacrolimus and mycophenolic acid. However, the long-term efficacy and safety of these unconventional strategies remains unknown.

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### INTRODUCTION

Appropriate immunosuppression is a key component of

successful kidney transplantation. It is generally accepted that more intensive immunosuppression is required initially to prevent acute rejection (AR) and graft loss from AR, and less immunosuppression is subsequently maintained to allow the recipient to tolerate allograft and to minimize the adverse effects of immunosuppressive drugs. Many transplant centers in the USA routinely use an antilymphocyte antibody peri-operatively as induction therapy in addition to a maintenance regimen. In the year of 2008, 81.5% of kidney transplant recipients were given one of the following antibody inductions: thymoglobulin (44.8%), basiliximab (17.8%), daclizumab (10.9%), alemtuzumab (10.7%), and other 18.5% of patients do not receive any antibody induction<sup>[1]</sup>. The modern maintenance typically consists of a combination of two of the three classes of agents, calcineurin inhibitor (CNI, tacrolimus or cyclosporine), mycophenolic acid (mycophenolate mofetil or enteric coated mycophenolate sodium) and mammalian target of rapamycin inhibitor (sirolimus or everolimus), with or without steroids<sup>[1]</sup>. In this review, we will discuss the controversial issue of various antibody induction therapies, which were studied on adult patients of different immunologic risk in the context of varying maintenance immunosuppressive regimens.

### OKT-3

OKT-3 is a murine monoclonal antibody against CD3 molecule. It depletes T cells by binding to the T-cell receptor-associated CD3 glycoprotein. Though historically used, it was never approved in the USA by the food and drug administration (FDA) as an induction agent. OKT-3 is associated with many side effects, including first-dose effect<sup>[2]</sup>, pulmonary edema<sup>[3]</sup>, nephropathy<sup>[4]</sup>, infection<sup>[5,6]</sup> and malignancy<sup>[7]</sup>. Antithymocyte globulin (ATG) preparations were demonstrated to be superior than OKT-3 in terms of decrease in the incidence of AR and better tolerability<sup>[8-10]</sup>. The use of OKT-3 was subsequently decreased and led to cessation of its production in 2009.

### ATG

There are two forms of ATG that are polyclonal immunoglobulins against human thymocytes from either horses (ATGAM) or rabbits (thymoglobulin). ATG binds to various cell surface markers, including CD2, CD3, CD4, CD8, CD11a and CD18, and leads to complement dependent lysis of lymphocytes. ATG as well as OKT-3 and alemtuzumab are often referred as lymphocyte-depleting antibodies. ATGAM was approved by FDA for both treatment and prevention of AR whereas thymoglobulin was only approved to treat AR episodes. ATG use is associated with cytokine release syndrome, myelosuppression and rarely anaphylactic reaction<sup>[11]</sup>. Several studies found that thymoglobulin was more effective in preventing AR and was associated with better graft survival than ATGAM<sup>[12-14]</sup>. Subsequently, ATGAM was used less frequently as induction therapy.

Dose of thymoglobulin induction has ranged from 1 to 4 mg/kg per day for 3 to 10 d. One study compared 3-d induction regimen ( $n = 40$ ) with the historic 7-d course ( $n = 48$ ). With 3-d course, thymoglobulin was administered at 3 mg/kg intra-operatively followed by 1.5 mg/kg on post-operative day 2 and 3. The 7-d course consisted of 1.5 mg/kg intra-operatively followed by same daily dose for next 6 d. Shorter initial hospital stay (6.1 d *vs* 8 d) and more profound lymphocyte depletion were observed in the 3-d group<sup>[15]</sup>. There was no difference in AR (5% *vs* 4.2%), graft survival (95% *vs* 98%) and patient survival (95% *vs* 98 %) at the end of 1 year in the 3-d *vs* 7-d group. Intraoperative administration of thymoglobulin was found to be associated with a lower incidence of delayed graft function (DGF) and shorter hospital stay<sup>[16]</sup>. Doses less than 3 mg/kg may not effectively prevent AR<sup>[16]</sup>. Higher dose and longer duration of induction was associated with increased risk of infection and lymphoma<sup>[17-21]</sup>. Therefore, the optimal dose of thymoglobulin induction might be a total of 6 mg/kg administered as 1.5 mg/kg per day in 3 to 5 d<sup>[17-21]</sup>.

To compare thymoglobulin *vs* placebo induction, 89 sensitized renal transplant recipients received induction with (47 patients) or without (42 patients) thymoglobulin. The maintenance regimen consisted of cyclosporin, steroids and azathioprine. At the end of 1 year, the incidence of AR was 38% in thymoglobulin group and 64% in the placebo group. Both graft survival (89% *vs* 76%) and graft function were better in thymoglobulin group than the placebo group<sup>[22]</sup>. Similar benefits with ATG induction were reported by a meta-analysis of seven comparative studies<sup>[23]</sup>. Further analysis indicated that ATG induction might reduce the risk of graft loss greater in sensitized patients with high panel-reactive antibody (PRA) than in unsensitized patients<sup>[24]</sup>.

These studies were performed in the era of less potent old maintenance immunosuppressives. The introduction of modern more potent maintenance drugs has successfully decreased the incidence of rejection and has improved graft survival<sup>[25-28]</sup>. The independent use of either mycophenolic acid<sup>[25,26]</sup> or tacrolimus<sup>[27,28]</sup> was found to have advantages over azathioprine or cyclosporine, respectively. In a 3-group comparative study with 6-mo follow up, AR was highest in the group receiving tacrolimus, azathioprine and prednisone without induction (25.4%) compared to the group receiving tacrolimus, azathioprine, prednisone and thymoglobulin induction (15.1%) and the group receiving cyclosporine, azathioprine, prednisone and thymoglobulin (21.2%)<sup>[29]</sup>. In the two thymoglobulin induction groups, tacrolimus arm had a lower incidence of AR than cyclosporine arm. The patient and graft survival were similar in all three groups. Both thymoglobulin groups had more side effects including leukopenia, thrombocytopenia and CMV infection. In the era of modern potent maintenance regimen including tacrolimus and mycophenolic acid, it is unlikely that ATG induction can still provide that much benefits as it was previously demonstrated in the context of less potent maintenance of cyclosporine and azathioprine.

## INTERLEUKIN-2 RECEPTOR ANTIBODY

Daclizumab and basiliximab are the two interleukin (IL)-2 receptor antibodies (IL-2R Ab). Daclizumab is a humanized antibody and basiliximab is a chimeric monoclonal antibody. Both bind to the  $\alpha$  chain of IL-2 receptor complex (CD25) expressed on activated T lymphocytes. This prevents the T cell activation and proliferation without causing cell lysis. Therefore, they are also known as non-depleting antibodies. IL-2R Ab was first introduced in 1997 and was FDA approved for induction therapy. They have the best safety profile compared to other available induction antibody without increased risk of infection or malignancy<sup>[30-32]</sup>.

IL-2R Abs have been subjected to numerous placebo-controlled, randomized trials, which have showed a reduction in AR rate compared with placebo (28% *vs* 42%)<sup>[33-36]</sup>. In a meta analysis, the risk of AR is significantly reduced in patients who received IL-2R Ab induction than in those with placebo at 6 mo (12 trials: relative risk 0.66, 95% CI: 0.59-0.74) and at 1 year (10 trials: relative risk 0.67, 95% CI: 0.60-0.75)<sup>[37]</sup>. The incidences of CMV infection and malignancy at 1 year were similar to placebo control<sup>[37]</sup>. Both IL-2R Abs have similar efficacy and safety profile, but basiliximab is administered as 2 doses within 4 d of transplantation, whereas daclizumab is administered as 5 doses over 8 wk<sup>[19,32]</sup>. This difference in convenience of administration led to more frequent use of basiliximab than daclizumab. Subsequently, Roche pharmaceuticals withdrew daclizumab from market in October 2008.

Our center's decade - long experience has indicated that basiliximab induction is safe and adequate for kidney transplant, including the high risk transplants, such as deceased donor kidney transplants in highly sensitized African Americans<sup>[38]</sup>, simultaneous kidney pancreas transplant in African Americans<sup>[39]</sup> and splitting single pediatric donor kidney transplant<sup>[40]</sup>, as long as the conventional triple regimen consisting of tacrolimus, mycophenolic acid and steroids are used as maintenance. A recent analysis based on USRDS data from 2000 to 2005 also indicated that both patient and graft survival were similar in African Americans and Caucasian patients using either thymoglobulin or IL-2R Ab induction<sup>[41]</sup>.

## IL-2 RECEPTOR ANTIBODY VS ATG

The safety and efficacy of thymoglobulin and basiliximab induction were compared in 278 high risk patients who received deceased donor kidneys<sup>[42]</sup>. High risk was determined according to the duration of cold ischemia and various other donor and recipient risk factors including donor age > 50 years, donation after cardiac death, donor with ATN or requiring high dose of inotropic support, repeat transplant, PRA > 20%, black race and one or more HLA mismatches. Both groups received cyclosporine, mycophenolate mofetil and prednisone as maintenance. At 12 mo, there were fewer biopsy-proven AR in the thymoglobulin group than in the basiliximab

group (15.6% *vs* 25.5%,  $P = 0.02$ ). Severe rejection, as indicated by the need for antibody treatment, was less frequent in thymoglobulin group than basiliximab group (1.4% *vs* 8.0%,  $P = 0.005$ ). The incidence of DGF (40.4% *vs* 44.5%,  $P = 0.54$ ), graft loss (9.2% *vs* 10.2%) and death (4.3% *vs* 4.4%) was similar in both groups. However the incidences of infection and malignancy were significantly higher in thymoglobulin group than basiliximab group. A 5-year follow-up of these patients showed that AR remained lower in thymoglobulin than basiliximab group, but graft and patient survival were still not different<sup>[43]</sup>. Similar result was also reported by Noël *et al*<sup>[44]</sup> in 227 high risk patients who received modern maintenance of tacrolimus, mycophenolate mofetil and corticosteroid. High risk was defined as PRA > 30% and/or peak PRA > 50%, loss of a first renal transplant to rejection within 2 years or history of two or more previous transplants. Compared to the daclizumab group, thymoglobulin group had lower incidence of AR (15.0% *vs* 27.2%), and steroid-resistant AR (2.7% *vs* 14.9%) and also delayed the time to AR (35 d *vs* 13 d) in 1 year<sup>[44]</sup>. However, there was no difference in either graft or patient survival. The number of bacterial infection per patient ( $2.5 \pm 1.8$  *vs*  $1.7 \pm 1.2$ ,  $P = 0.01$ ) and the incidence of CMV infection (18.6% *vs* 10.5%,  $P = 0.09$ ) was significantly higher in the thymoglobulin group than in the daclizumab group. These clinical trials show that thymoglobulin induction reduces the risk of AR, but it increases the risk of infection and possible malignancy. There is no convincing clinical evidence of superior graft or patient survival with thymoglobulin induction than the IL-2R antibody induction in high-risk patients.

Using SRTR database, Patlolla *et al*<sup>[45]</sup> analyzed a total of 48 948 recipients of first renal transplants who were discharged on CNI (cyclosporine or tacrolimus) and anti-metabolite (mycophenolic acid or azathioprine). Induction with IL-2R Ab (basiliximab or daclizumab,  $n = 17\,472$ ) was associated with a reduction in both AR (odds ratio 0.81, 95% CI: 0.75-0.87) and graft loss (hazard ratio 0.90, 95% CI: 0.84-0.95) compared with no antibody induction ( $n = 22\,008$ ). The greater the HLA mismatch, higher the efficacy of IL-2R Ab in reducing AR. Compared to IL-2R Ab induction, lymphocyte - depleting antibody (thymoglobulin, ATGAM or OKT-3,  $n = 9468$ ) was associated with lower risk of AR (OR: 0.90, 95% CI: 0.83-0.99) at 1 year, but not associated with any better graft survival (OR 1.08, 95% CI: 1.00-1.18). Several studies directly compared thymoglobulin with IL-2R Ab induction in patients with low immunologic risk<sup>[46-48]</sup>. Similar rejection rate and graft survival, but higher incidence of infection was reported in those received thymoglobulin than IL-2R Ab induction. These clinical data, taken together with other trials comparing IL-2R Ab induction with placebo<sup>[33-37]</sup> supports use of IL-2R Ab rather than thymoglobulin for induction in low risk patients.

## ALEMTUZUMAB

Alemtuzumab is a humanized anti-CD52 monoclonal



antibody, which triggers the antibody-dependent lysis of lymphocytes (both B and T cells), monocytes and NK cells. Alemtuzumab is FDA approved for treating B cell lymphomas. It was first introduced to kidney transplant by Calne *et al.*<sup>[49]</sup> in late 1990s. As an induction agent, it produces a profound depletion of lymphocytes and is associated with more frequent and severe adverse effects, such as neutropenia, thrombocytopenia, autoimmune hemolytic anemia and other autoimmune diseases<sup>[50,51]</sup>. However, it did not appear to affect the incidence of recurrent glomerulonephritis<sup>[52]</sup>. Two doses of alemtuzumab were initially administered for induction<sup>[53,54]</sup>. Due to its profound immunosuppression, single dose (30 mg, given intraoperatively) has been subsequently studied<sup>[55,56]</sup>. It is also hoped that alemtuzumab induction could permit patients to be maintained on less intensive immunosuppression, such as tacrolimus monotherapy<sup>[57,58]</sup>, steroid-free regimen<sup>[59,60]</sup>, or lower doses of tacrolimus and mycophenolic acid<sup>[59,61]</sup>.

Margreiter *et al.*<sup>[57]</sup> assessed the efficacy of alemtuzumab induction with tacrolimus monotherapy ( $n = 65$ ) as compared to no induction with tacrolimus, mycophenolate mofetil and steroid maintenance ( $n = 66$ ) for deceased donor kidney transplant. At 12 mo, the incidence of AR was not statistically different (20% *vs* 32%,  $P = 0.09$ ). The graft and patient survival were similar, but alemtuzumab group had more CMV infection. This protocol was also studied in living donor kidney transplant by Tan *et al.*<sup>[62,63]</sup>. A total of 205 living donor recipients were treated with alemtuzumab induction followed by tacrolimus monotherapy and 47 controls were treated with conventional triple therapy of mycophenolate, tacrolimus and prednisone without induction. At 1 year, the incidence of AR was much lower in the alemtuzumab group (6.8% *vs* 17%,  $P < 0.05$ )<sup>[62]</sup>. The 1, 2, and 3-year patient survival (99%, 98% and 96.4%) and the graft survival (90.8%, 93.3% and 86.3%) in the alemtuzumab group, are similar to the SRTR data for living donor kidney transplantation<sup>[63]</sup>.

Induction with alemtuzumab ( $n = 123$ ) and basiliximab ( $n = 155$ ) were compared in a steroid-free maintenance consisting of mycophenolate acid and tacrolimus<sup>[64]</sup>. Early rejection ( $< 3$  mo) rates were higher in the basiliximab group (11.6% *vs* 4.1%) but were equal at 1 year in the two groups (13.5% *vs* 14.9%,  $P = \text{NS}$ ). The 1-year death censored graft survival was 99.2% for the alemtuzumab and 99.4% in the basiliximab group ( $P = \text{NS}$ ). The incidence of CMV disease (4% *vs* 5%) and malignancy (2 recipients in each group) were also similar in the two groups. Therefore, in steroid-free maintenance, alemtuzumab induction is associated with lower incidence of early rejection, but similar graft survival compared to basiliximab induction.

## ALEMTUZUMAB VS BASILIXIMAB VS THYMOGLOBULIN

These three antibody induction agents were first compared by Ciancio *et al.*<sup>[59]</sup> in 90 deceased donor kidney

transplants. Maintenance immunosuppression was tacrolimus (target trough level of 8-10 ng/mL), mycophenolate mofetil (1000 mg twice daily) and prednisone in thymoglobulin and daclizumab groups, while alemtuzumab group received lower doses of tacrolimus (target trough level of 4-7 ng/mL) and mycophenolate mofetil (500 mg twice daily). At 1 year, there was no significant difference in the three groups for AR, graft survival or patient survival. At 2 years, cumulative incidences of AR were 20%, 23% and 23% in thymoglobulin, alemtuzumab and daclizumab groups, respectively<sup>[61]</sup>. The overall patient and graft survival were similar, but there was a trend towards worse death censored graft survival and more chronic allograft nephropathy in alemtuzumab group<sup>[61]</sup>. In another study of rapid steroid withdrawal in a total of 474 kidney recipients, 139 high risk patients (African American, PRA  $\geq 20\%$  or re-transplants) were induced with alemtuzumab or thymoglobulin, while 335 low risk patients (non African American, PRA  $< 20\%$  or primary transplant) were induced with alemtuzumab or basiliximab<sup>[60]</sup>. At 2 years, alemtuzumab induction has lower incidence of AR than basiliximab (8.9% *vs* 21.7%,  $P < 0.05$ ) for low risk patients. The high-risk patients experienced same rejection rates with either thymoglobulin or alemtuzumab induction (13% in both groups). Patient and graft survival at 2 years were similar between the groups in both high risk patients (98.6% *vs* 93% and 92.2% *vs* 88.4%, alemtuzumab *vs* thymoglobulin,  $P = \text{NS}$ ) and low risk patients (97.4% *vs* 98% and 96.2% *vs* 92.3%, alemtuzumab *vs* basiliximab,  $P = \text{NS}$ ). A 3-year follow up showed similar results in terms of lower incidence of AR with alemtuzumab than basiliximab (10% *vs* 22%,  $P = 0.003$ ) in low risk patients, while no difference in AR between alemtuzumab and thymoglobulin (18% *vs* 15%,  $P = 0.63$ ) in high risk patients<sup>[65]</sup>.

From these data, alemtuzumab induction appears to be more successful than other induction for unconventional protocols, such as steroid withdrawal, tacrolimus monotherapy or lower doses of tacrolimus and mycophenolic acid. However, these studies are small, short-term and should be considered as experimental. The long-term efficacy of these protocols remains to be vigorously investigated<sup>[53,61,66]</sup>. One obvious concern is that lymphocytes could recover from the initial depletion if insufficient maintenance immunosuppression is left over long term, which potentially leads to development of AR and/or chronic rejection. Late development of *de novo* donor specific antibodies (DSA) is increasingly recognized as an independent and detrimental factor for accelerated transplant glomerulopathy and graft loss<sup>[67,68]</sup>.

## RITUXIMAB

Rituximab is a chimeric monoclonal Ab against CD20, which is expressed on the majority of B cells. It was first approved in 1997 for refractory B cell lymphomas and it is increasingly applied for autoimmune diseases. In the realm of kidney transplant, rituximab has been used for the treatment of AMR and desensitization in

ABO and/or HLA incompatible transplants<sup>[69,70]</sup>. Takagi *et al*<sup>[70]</sup> reported rituximab induction in desensitization of 78 ABO and/or HLA incompatible transplants, all of them also received 3-4 sessions of double-filtration plasmapheresis before transplant. Compared with the non-rituximab group of 66 compatible transplants, rituximab group had significantly lower incidence of ACR (8.2% *vs* 23.3%,  $P < 0.05$ ), but not higher incidence of AMR (6.8% *vs* 8.3%,  $P = 0.75$ ). Anti-HLA Ab to class 1 and class 2 were depleted by 70% and 83%, respectively for more than 2 years after rituximab induction. The incidences of CMV infection (26% *vs* 29%,  $P = 1.0$ ) or leukopenia (23% *vs* 14%,  $P = 0.25$ ) were not different, and the 2-year survival rates of patient (100% *vs* 98%,  $P = 0.28$ ) and graft (99% *vs* 100%,  $P = 0.91$ ) were excellent in both groups<sup>[70]</sup>. Therefore, rituximab appears to be a safe and effective induction Ab for the desensitization protocol of ABO or HLA incompatible transplants.

In the setting of non-desensitization, Clatworthy *et al*<sup>[71]</sup> reported that 5 of 6 patients (83%) induced with rituximab had ACR in the first 3 mo after transplant as compared with 1 of 7 patients (14%) induced with daclizumab ( $P = 0.01$ ). However, Tydén *et al*<sup>[72]</sup> reported a randomized, doubleblind multicenter study that included 68 rituximab and 68 placebo patients. All patients received conventional maintenance of tacrolimus, mycophenolic acid and steroids. During the first 6 mo, there were 10 treatment failure (defined as AR, graft loss or death) in rituximab group *vs* 14 in placebo group ( $P = 0.35$ ). There was a tendency toward fewer AR (8/68 *vs* 12/68,  $P = 0.32$ ) and milder AR without increase in infections or leukopenia in the rituximab group. Long-term study is needed to further determine the benefits of rituximab induction for non-sensitized patients.

## OTHER CONSIDERATION

Apart from the immunologic risk, many other medical and physical factors should also be considered in the choice of induction therapy. Depleting antibody (thymoglobulin, ATGAM, OKT-3 and alemtuzumab) induction should be avoided in patients with history of malignancy, severe viral infection (including HIV, HBV or HCV), hematological disorder of leucopenia or thrombocytopenia and elderly with cardiac or pulmonary comorbidities<sup>[73-75]</sup>. For these patients, we do not use any antibody induction if they do not have high immunologic risk, and we use IL-2R Ab induction (not lymphocyte depleting antibody) for those who do have high immunologic risk. A recent study of 150 HIV-infected patients who underwent kidney transplant indicated that ATG induction significantly increased the risk of graft loss (HR 2.5, 95% CI: 1.1-5.6,  $P = 0.03$ ). ATG induction was also associated with twice as many serious infections per follow-up year as patients received IL2R Ab induction or no induction (0.9 *vs* 0.4,  $P = 0.002$ )<sup>[74]</sup>. Another study reported that 2-year patient survival was less than 50% in the elderly (more than 60 years old) who had DGF and received thymoglobulin induction<sup>[75]</sup>.

The financial costs of antibody induction therapies are significantly different. In US, the average whole sale price for the typical dose of alemtuzumab (30 mg  $\times$  1 dose) is \$1982.70; basiliximab (20 mg  $\times$  2 doses) is \$5338.66; while thymoglobulin (1.5 mg/kg  $\times$  4 doses for a 70 kg patient) costs \$10 200.00<sup>[76]</sup>. A financial analysis indicated that IL-2R Ab (basiliximab/daclizumab) was more cost effective than placebo (no induction) or induction with lymphocyte-depleting antibody (OKT3/ATG/ATGAM)<sup>[77]</sup>.

## CONCLUSION

Published data support the usage of antibody induction therapy in adult patient with immunologic risk to reduce the incidence of AR and possible graft loss from rejection. However, the choice of antibody remains controversial. Antibody selection should be guided by a comprehensive assessment of immunologic risk of recipient and donor organ, patient comorbidities, financial burden, and more importantly, the maintenance immunosuppressive regimen. Lymphocyte-depleting antibody is recommended for those with high immunologic risk as outlined in the 2009 KDIGO clinical practice guidelines<sup>[78]</sup> (sensitized patient, presence of DSA, ABO incompatibility, high HLA mismatches, DGF, cold ischemia time  $> 24$  h, African-American ethnicity, younger recipient age, older donor age), though it increases the risk of infection and malignancy. For low risk patients, IL-2R Ab induction reduces the incidence of AR and graft loss without much adverse effects, making its balance favorable in most patients. IL-2R Ab induction should also be used in the high risk patients with other medical comorbidities that preclude usage of any lymphocyte-depleting antibody safely. We believe that many patients with very low risk (non-sensitized, Caucasian, Asian, well HLA matched, living related donor transplant) may be induced with intravenous steroids without using any antibody, as long as combined potent immunosuppressives are kept as maintenance. In these patients, benefits with antibody induction may be too small to outweigh its adverse effects and the financial cost. Rituximab induction is useful in desensitization protocols for ABO and/or HLA incompatible transplants. Alemtuzumab induction might be more successful than other antibody induction for adopting less intensive maintenance protocols, such as steroids withdrawal, tacrolimus monotherapy or lower doses of tacrolimus and mycophenolic acid. However, the long-term safety and efficacy of these unconventional strategies remains to be determined.

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