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KIDNEY TRANSPLANTATION (M HENRY, SECTION EDITOR)

Biologics in Transplantation (Anti-thymocyte Globulin, Belatacept, Alemtuzumab): How Should We Use Them?

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Abstract
Purpose of Review The use of immunosuppressive agents for induction and maintenance therapies continues to vary widely among countries and transplant centers. This review will consolidate the published body of evidence addressing the effectiveness and safety of the use of three biological agents: anti-thymocyte globulin, alemtuzumab, and belatacept in adult kidney transplant recipients.
Recent Findings Clinical evidence clearly supports the use of Thymoglobulin in high immunological risk patients, while its benefit in low immunological risk patients remains controversial. Alemtuzumab has the advantage of easy administration with comparable efficacy to Thymoglobulin but concerns regarding increased risk for late rejection. Belatacept is the newest biological agent. It is associated with higher glomerular filtration rates compared to cyclosporine. Belatacept has not been compared to tacrolimus or studied in high immunological risk patients in sufficiently large numbers.
Summary Tailoring immunosuppressive therapy to patient's characteristics and immunological risk is the key for successful transplantation.

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Introduction

Immunosuppressive agents used in kidney transplantation can be broadly classified into induction agents and maintenance therapy. This review will consolidate the published evidence of trials addressing the effectiveness and safety of the use of three biological agents: anti-thymocyte globulin, alemtuzumab, and belatacept in adult kidney transplant recipients.

Induction immunosuppressive therapy aims to prevent acute allograft rejection with minimal infection and toxicity. The optimal choice of induction agent remains controversial. There is significant heterogeneity in use among countries and transplant centers based on risk-benefit for each patient [1, 2].

Anti-thymocyte Immunoglobulins

Anti-thymocyte globulins (ATG) are polyclonal immunoglobulins extracted from sera of previously immunized rabbits (rATG; Thymoglobulin and ATG-Fresenius) or horses (eATG; ATGAM). These globulins target numerous different antigens on the surface of multiple leukocyte subsets and nonimmune cells such as the endothelial cells. Dose-dependent T cell depletion in the peripheral blood, spleen and bone marrow, but not the thymus, is thought to be the principle mechanism of action of ATG [3]. Regulatory T cell (Treg) expansion after treatment with rATG has also been demonstrated in vitro as well as

in vivo, a phenomenon that is believed to contribute to the protective role of rATG against rejection [4, 5].

ATG can also control B cell activation and antibody production by interfering with the necessary T-B cell interaction and the lysis of B cells by binding to cell surface proteins shared between the B and T lymphocytes.

The eATG, ATGAM, has been largely abandoned in favor of Thymoglobulin which is better tolerated and more efficacious in the prevention and treatment of acute rejection [6•, 7]. Hence, eATG will not be discussed here.

There are two available preparations of rabbit ATG: Thymoglobuin (rATG) and ATG-Fresenius (ATG-F). Thymoglobulin was developed by using human thymocytes as the immunogen, while ATG-F was developed using the Jurkat T-acute lymphoplastic leukemia cell line to immunize rabbits. The two preparations have different composition and immunomodulatory effects [8]. There is limited and mixed data comparing the two as induction agents in renal transplantation. A retrospective study compared ATG-F to rATG in 47 patients and found both preparations to be comparable in terms of acute graft rejection, 3-month graft and patient survival, and safety profile [9]. In another retrospective study limited to patients who received kidney donation after cardiac death, Thymoglobulin was associated with decreased risk for acute rejection (9.6 vs 19.4%; $P = 0.035$), decreased incidence of delayed graft function (DGF), and decreased duration of DGF (11.7 vs 16.1 days; $P = 0.028$) [10] compared to ATG-F.

Fresenius ATG is not approved for use in the USA. Thymoglobulin is the induction agent currently used by the majority of kidney transplant centers (>60%) in the USA and will be the focus of this chapter. Despite the widespread use of Thymoglobulin, consensus regarding the optimal dosage and administration protocol continues to be lacking, with significant variation between transplant centers [11–13].

Thymoglobulin Induction in Low Immunological Risk Patients

The use of Thymoglobulin in low-risk recipients is controversial. To date, no large, randomized clinical trial has compared Thymoglobulin to no induction in low immunological risk patients in the current era of effective maintenance immunosuppressive therapy with tacrolimus (TAC), mycophenolate mofetil (MMF), and prednisone (PDN). Two short-term European randomized clinical trials demonstrated reduced rate and severity of biopsy-proven acute rejection (BPAR) with rATG induction in deceased donor kidney transplant recipients when compared to the no induction arm [14, 15]. Both trials consisted mostly of low-risk patients (>90% Caucasian, first transplant, PRA <50%) and used maintenance therapy with TAC/azathioprine/prednisone. There was no difference in the overall graft or patient survival at the expense of increased risk for cytomegalovirus (CMV) infection, leukopenia, and thrombocytopenia in the Thymoglobulin arm. Noticeably, both trials used much higher doses of Thymoglobulin compared to what is commonly used nowadays (12.5 mg/kg total dose vs 3–6 mg/kg) with no routine CMV prophylaxis. Additionally, the maintenance immunosuppressive regimen was azathioprine not MMF based, which might have affected the risk for rejection in the no induction arm.

When compared to basiliximab, an interleukin-2 receptor antagonist (IL-2RA), Thymoglobulin induction shows similar results of reducing risk of BPAR without an effect on the overall graft or patient survival. A 2009 Cochrane meta-analysis included 71 randomized clinical trials comparing different induction therapy [16]. The overall cohort consisted mostly of low immunological risk recipients with 72% being first-time transplants. Eighteen of the 71 included studies compared IL-2RA to ATG. There was no difference in graft loss at any point of time or in the rate of acute rejection diagnosed clinically. However, ATG therapy decreased the rate of BPAR (RR 1.30, 95% confidence interval (CI) 1.01–1.67).

Thymoglobulin in High Immunological Risk Patients

The benefit of Thymoglobulin induction is less disputable in patients characterized as high immunological risk. Two randomized controlled trials have shown the advantage of Thymoglobulin induction in such patient population. The first, by Brennan et al., was a multicenter international randomized trial of 278 recipients of deceased donor kidney transplantation at high risk for delayed graft function and/or acute rejection. Patients were randomized to induction with Thymoglobulin or basiliximab followed by maintenance cyclosporine (CsA), MMF, and prednisone. The rate of BPAR and rejection requiring treatment with depleting agents in US patients were significantly lower in the Thymoglobulin group at 1 year (15.6 vs. 25.5%; $P = 0.02$) and 5 years (15 vs 27%; $P = 0.03$), but not at 10 years (21 vs 32.8%; $P = 0.07$) [17–19]. The second randomized controlled trial, by Noël et al., enrolled 227 high immunological risk patients (mean panel reactive antibody of >30%) in France and Belgium and used a more modern maintenance immunosuppressive therapy with tacrolimus, MMF, and prednisone [20]. This study demonstrated similar results of reduced BPAR and steroid-resistant rejection at 1 year (15 vs 27%; $P = 0.016$) and 5 years (14 vs 26%; $P = 0.035$) [21] compared to IL-2RA (Daclizumab) induction. Both studies showed no difference in long-term graft or patient survival between the study groups.

A retrospective analysis using the national scientific registry of transplant recipient data (SRTR) evaluated the clinical outcomes in adult recipients of kidney re-transplantation between 2003 and 2011 [22]. Compared to patients induced with

Thymoglobulin, the no induction group had 82% greater adjusted likelihood ratio of early acute rejection (adjusted odd ratio (AOR) 1.82, 95% CI 1.48–2.25). IL-2RA induction was associated with over twofold likelihood of early acute rejection (AOR 2.4, 95% CI 1.76–3.28). There was no difference in terms of patient or graft survival between the Thymoglobulin and IL-2RA groups. The authors concluded that given the risks and costs associated with the treatment of acute rejection episodes, the reduction in early graft rejection supports the use of Thymoglobulin induction for high immunological risk patients.

Thymoglobulin and Corticosteroids Withdrawal

Use of rATG may be superior to IL-2RA or no induction with early steroid withdrawal. Woodle et al. compared early steroid withdrawal (within 7 days post operatively) to chronic low-dose steroids in patients who received antibody induction (IL-2RA or rATG) and TAC/MMF maintenance immunotherapy [23•]. There was no difference in the primary composite outcome of death, graft loss, and moderate/severe acute rejection at 5 years between the two groups, but a subgroup analysis showed numerically higher BPAR in the IL-2RA group (24.4%) compared with rATG (14,4%; $P = 0.09$). Two recent SRTR registry analysis by Tanriover et al. evaluated acute rejection rates and graft outcomes per induction regimen among recipients of deceased donor and living donor kidney transplants maintained on TAC/MMF regimen [24, 25]. Both studies showed similar results: rATG induction was associated with less BPAR and better graft survival compared to IL-2RA in patients treated with early steroid withdrawal. In contrast, a recent, open label, multicenter clinical trial from Germany (Harmony study) compared Thymoglobulin with early steroid withdrawal to IL-2RA induction with either early steroid withdrawal or chronic steroid therapy [26]. The study found no significant difference in the primary outcome of acute rejection between the Thymoglobulin group (9.9%) and either IL-2RA groups (10.6% for steroids maintenance, $P = 0.75$; 11.2% early steroid withdrawal, $P = 0.87$). However, the patient cohort in the study consisted mostly of very low immunological risk recipients (>98% Caucasian, >86% PRA 0%).

Safety

Rabbit-ATG induction has historically been associated with increased risk for CMV infection and malignancy. The use of universal CMV prophylaxis has significantly decreased the risk for CMV infection and improved graft survival [27]. The increased risk for malignancy, especially post-transplant lymphoproliferative disorders (PTLD), also appears to be decreasing. Registry analyses that analyzed patients from the 1990s and 2000s when much higher doses of ATG were routinely used and included different lymphocyte depleting agents (rAGT, eATG, alemtuzumab) did show increased risk for PTLD with lymphocytes depletion [28–30]. More recent registry analyses evaluating patients treated with Thymoglobulin induction using more contemporary dosages have failed to show an increase in PTLD compared to the general kidney transplant population [31, 32]. These findings indicate that the increase risk for malignancy is proportionally related to the overall degree of immunosuppression and the lack of antiviral prophylaxis and not induction with lymphocyte depleting agents alone.

Our Practice and Recommendations

It is unlikely that there will be a large randomized clinical trial (RCT) comparing rATG to no induction or IL-2RA in patients maintained on TAC/MMF/Pred. It is important to realize that the use of potent induction with rATG allows for immunosuppression reduction not only of steroids but the CNI and antimetabolite. This is not captured well in the reports of RCTs or registry analyses. The 2009 KDIGO guidelines for the care of kidney transplant recipients recommended that induction therapy be a routine part of the immunosuppressive regimen in kidney transplant recipients and that IL-2RA be the first line therapy (grade 1B) while lymphocyte depleting agents be used selectively in high immunological risk patients (grade 2B) [33]. We agree with the KDIGO guidelines regarding the use of rATG or other lymphocyte depleting agents in high immunological risk patients as the clinical evidence based on randomized controlled trials shows clear benefit in this patient population. Early corticosteroid withdrawal should probably be considered as another high-risk immunological situation in which there is a clear trend toward benefit with rATG induction compared to IL-2RA.

The recommendation regarding the use of IL-2RA routinely as a first line agent needs to be reviewed in the light of the current clinical evidence. The KDIGO recommendations were based on the 2009 Cochran meta-analysis that included studies conducted mostly in the 1990s and 2000s with cyclosporine and azathioprine being the major component of maintenance immunotherapy. This makes the results poorly applicable to the current TAC/MMF era. Moreover, mounting evidence suggest that in low risk patients, IL-2RAs do not provide advantages over no induction in terms of acute rejection or graft survival [24, 25, 34, 35]. This suggests that no induction therapy in low-risk patients maintained on TAC/MMF/Pred is reasonable. With the reduced concerns regarding rATG safety in terms of malignancy and CMV infections, another approach would be the use of low dose rATG. In our center, we use rATG induction for all kidney transplant recipients with an immunological risk-based dosing, (Fig. 1) except for two haplotype-matched siblings.

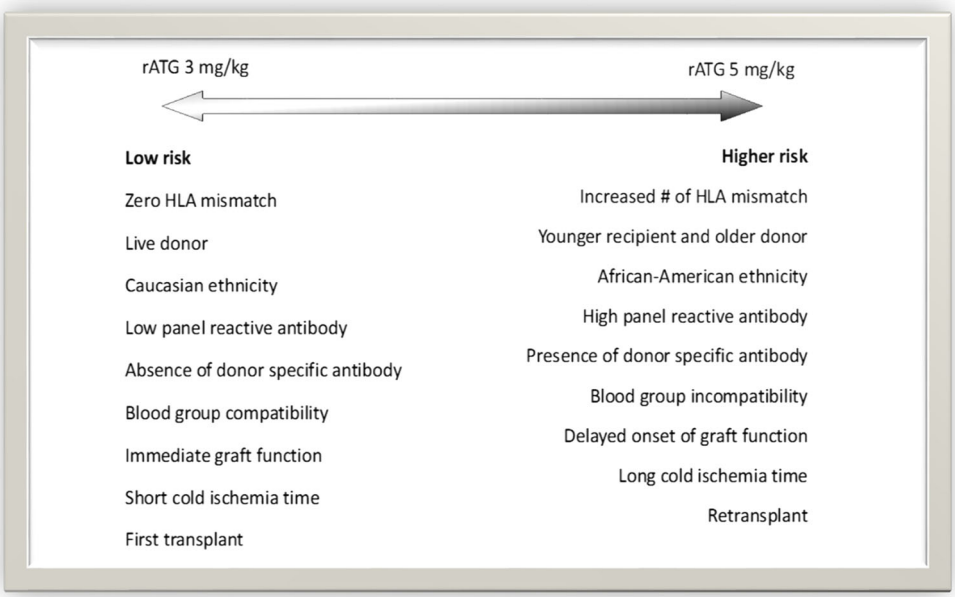

Fig. 1 Induction therapy choice based on risk assessement. Figure reproduced from Hardinger et al., *Transplant International,* with permission from John Wiley and Sons

Alemtuzumab

Alemtuzumab (Campath) is approved by the US Food and Drug Administration for the treatment of B-cell chronic lymphocytic leukemia (B-CLL). It has been used off label for induction therapy and in the treatment of acute rejection in transplantation [36]. As of September 2012, alemtuzumab is no longer commercially available in the USA but is provided by its manufacturer through a special distribution program.

Alemtuzumab is a humanized IgG-1 monoclonal antibody that binds to CD52, an antigen present on the surface of B and T lymphocytes, a majority of monocytes, macrophages, natural killer cells, and a subpopulation of granulocytes. Alemtuzumab binding to CD52 triggers an antibody-dependent cellular-mediated lysis of the cell. It is given intravenously as a one-time dose of 30 mg over 2 h. The subcutaneous route has also been studied, although this method of administration is not FDA approved [37].

Alemtuzumab vs Anti-thymocyte for Induction Therapy

A Large, multicenter, 3-year, randomized trial stratified patients by rejection risk: low risk (alemtuzumab vs. basiliximab, n = 335) or high risk (alemtuzumab vs. rATG, n = 139) [38]. All patients received tacrolimus, mycophenolate mofetil, and early steroid withdrawal. The rate of BPAR was significantly lower in the alemtuzumab group than in the conventional-therapy group (low and high risk combined—13 vs. 20%; P = 0.03). However, this benefit did not translate to improved graft survival or improved renal function. In addition, the apparent superiority of alemtuzumab was restricted to low-risk patients (BPAR 10 vs. 22%; P = 0.003). Among high-risk patients, alemtuzumab and rATG had similar efficacy (BPAR 18 vs. 15%; P = 0.53). In both the low- and high-risk groups, there was a trend toward late rejection in the alemtuzumab arm, an observation reported in several other studies [39, 40].

Different results were seen in a large, single-center study that compared alemtuzumab with rATG (n = 222) in low- and high-risk kidney alone, kidney-pancreas, pancreas after kidney, or pancreas alone transplants [41]. BPAR episodes occurred in 14% of alemtuzumab patients compared with 26% of rATG patients (P = 0.02), with no difference between low- and high-risk patients. Importantly, the study used a regimen of alternate-day rATG dosing rather than standard daily dosing, and tacrolimus levels were lower at 5 days post-transplantation in the rATG group (4.1 vs. 5.7 mg/dl; P = 0.01), likely contributing to higher rejection rates in the rATG group.

Morgan et al. published a meta-analysis and included 10 RCTs with a total of 1223 patients [42]. Studies were grouped by induction regimens. Alemtuzumab induction had a lower risk of BPAR compared to induction with basiliximab and daclizumab combined (RR 0.54; 95% confidence interval 0.37–0.79; P < 0.01). No significant difference was observed in the risk of BPAR when alemtuzumab induction was compared with rATG or ATG-Fresenius S (RR 0.79; 95% CI 0.52–1.21; P = 0.28). There was no difference in graft loss, DGF, patient death, and new-onset diabetes mellitus after transplantation when alemtuzumab was compared with IL-2RAs or rATG induction.

Another meta-analysis by Zhang et al. including six RCT found a lower incidence of ABMR with alemtuzumab compared to other induction regimens including rATG (RR 0.63;

CI 0.45–0.87; $P = 0.005$) [43]. This difference was lost when only high-risk patients were analyzed (RR 0.86; CI 0.48–1.55; $P = 0.62$).

Alemtuzumab Induction Therapy and Immunosuppression Minimization

Due to its profound lymphoid depleting properties, alemtuzumab has been considered as an agent that can produce long-lasting donor-specific hyporesponsiveness that allows reduction in maintenance immunosuppressive therapy. Various immune-minimization strategies have been tried with most studies demonstrating inferior outcomes [40, 44–47].

Ciancio et al. performed two separate prospective randomized trials and published combined results. In both trials, they compared reduced TAC and MMF dose coupled with corticosteroid avoidance in the alemtuzumab arm to standard maintenance therapy [44]. Statistically significant higher BPAR, higher biopsy-proven chronic allograft nephropathy, lower mean eGFR at 60 months, and lower death censored graft survival were noted in the alemtuzumab arm. Similar results were found in the single-center retrospective study comparing the outcomes of alemtuzumab and minimization therapy to r-ATG and standard triple immunotherapy [40].

The efficacy and safety of alemtuzumab induction with reduced CNI exposure was compared with non-depleting antibody induction (basiliximab) followed by standard CNI exposure in the 3C study [45]. At 6 months, alemtuzumab induction was associated with 58% proportional reduction in BPAR. Long follow-up date was not available.

Adverse Effects

There have been conflicting reports regarding the effect of alemtuzumab on infection in transplantation. A higher incidence of polyoma virus (BK) infection was observed in alemtuzumab group compared with basiliximab in 3C study (8 vs 4%; HR 1.92, CI 1.06–3.45; $P = 0.03$) [45]. Similarly, Saull et al. reported a significantly higher incidence of BK nephropathy with alemtuzumab compared to Thymoglobulin [46]. However, the Northwestern University transplant group and Cannon et al. reported incidences of BK viremia in concordance with other studies [48, 49].

Reports appear to be more concordant regarding the overall increased risk of CMV infection with alemtuzumab therapy [50–52] though some studies still report no increased incidence [37, 53].

Segev et al. [54] analyzed a total of 111,857 kidney recipients (1987–2009) entered in the Transplant Cancer Match Study which links the SRTR and United States Cancer Registries. Alemtuzumab induction was associated with increased risk of non-Hodgkin lymphoma, virus-related cancers, and colorectal and thyroid cancer. Conflicting results of no increased cancer risk were reported by Puttarajappa et al. among 1350 kidney transplant recipients followed over 4.5 years [55].

Belatacept

Belatacept is a fusion protein that consists of the extra cellular domain of the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and the FC fragment of human IgG1. It selectively binds to CD80 and CD86 antigens on the surface of the antigen presenting cells (APC) and inhibits the necessary T-cell co-stimulation signal that results from the interaction between CD28 on the T-cell and CD80/CD86 on the APCs (Fig. 2). The first phase II study to evaluate the utility of belatacept in kidney transplant was published in 2005 [56]. The study randomized 218 deceased and living donor patients, of which 89% (193) were considered at low immunological risk, to a more intensive (MI) or less intensive (LI) regimen of belatacept or to cyclosporine (CsA). Induction was achieved with basiliximab. There was no difference in the primary outcome of acute graft rejection in the first 6 months or the secondary outcome of graft and patient survival at 6 and 12 months, but both belatacept groups had significantly higher estimated glomerular filtration rate (eGFR) at 12 months (66.3 vs 62.1 vs 53.5 ml/min/1.73 m^2; $P = <0.05$). Five years later, the phase III studies of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study) [57•] and in recipients of extended criteria donors (BENEFIT-EXT study) were published [58]. Both studies had a similar design to the 2005 Vincent et al. trial and included mostly low-risk Caucasian patients. In the BENEFIT trial, 58% of donors were living donors. Patient and graft survival at 12 months were similar across all study groups despite higher incidence and grade of acute rejection in the belatacept groups (MI 22%, LI 17%, and cyclosporine

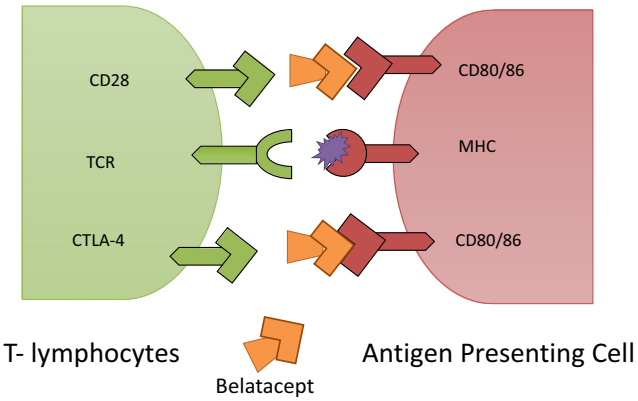

Fig. 2 Belatacept mechanism of action

7%) in patients in the BENEFIT trial. Belatacept was again associated with significantly superior graft function. The US Food and Drug Administration approved belatacept in 2011, partially due to the 3-year data of the BENEFIT [59] and BENEFIT-EXT [60] studies that showed consistent results of equal graft and patient survival but superior renal function (MI 65.2, LI 65.8, CsA 44.4 ml/min/1.73 cm^2 in the BENEFIT trial; MI 42.7, LI 42.2, CsA 31.5 ml/min/cm^2 in the BENEFIT-EXT). A strong safety signal was recognized during the two phase III studies. There was an increased incidence of PTLD, predominantly involving the central nervous system, in the belatacept groups. This was later found to be limited to patients who have Epstein Barr virus (EBV) negative serology and resulted in FDA approval of the less intensive belatacept regimen for use only in patients who are EBV seropositive.

The BENEFIT and BENEFIT-EXT cohorts were followed for up to 86 months (7 years) post transplantation [61, 62]. Interestingly, at 7 years, belatacept was associated with 43% reduction in the risk of death or graft loss in patients of living and standard donor kidneys of the BENEFIT trial (hazard ratio (HR) 0.57; 95% CI 0.35–0.95; $P = 0.02$), but no similar survival advantage was found in recipients of extended-criteria donor kidneys in the BENEFIT-extend trial. The mean eGFR in both belatacept groups did not only remain superior compared to the cyclosporine group but also increased over time. In the BENEFIT study, the mean eGFR increased by +0.20 ml/min/1.73 m^2 per year in the MI group and +0.38 ml/min/1.73 m^2 per year in the LI group while decreased by −1.92 ml/min/1.73 m^2 per year in the cyclosporine group (95% CI −2.51 to −1.32). Similar findings were also demonstrated in the BENEFIT-EXT study. This finding of improved graft function is surprising and hard to be understood as there is no clear physiological reason to explain such a rise in graft function over time. An important finding highlighted in both trials was the reduced incidence of de novo donor specific antibodies in the belatacept groups. This could be the result of costimulatory blockade preventing the T-B cell interaction required for full activation of B cells by de novo antigens, but it could also reflect the improved medication compliance inherent to the monthly infusion over daily oral tablets. Additionally, cyclosporine is known to reduce exposure to mycophenolate, which might have also contributed to the higher incidence of DSA in the CsA group.

Despite the positive and promising results of the BENEFIT and BENEFIT-EXT trials, their results should be interpreted in light of their limitations. First, the studies did not compare belatacept to the current standard tacrolimus-based maintenance immunotherapy. Second, both studies consisted mostly of low immunological risk patients, and in the case of the BENEFIT patients, the majority were living donor Caucasian recipients. Lastly, in the 7-year follow-up studies, patients who dropped out, crossed over, or were lost to follow-up were excluded from the final analysis.

Tacrolimus has been shown to be superior to cyclosporine in terms of graft survival and function [63]. To date, no major trial has compared belatacept to TAC. A small, open-label, randomized, multicenter exploratory study compared belatacept to TAC in a steroid-free regimen [64]. The study randomized 89 low immunological risk patients in 1:1:1 fashion to belatacept-MMF, belatacept-sirolimus, and TAC-MMF after induction with Thymoglobulin. The incidence of acute rejection and graft loss at 12 months were numerically higher in the belatacept groups but not statistically significant. eGFR at 12 months was 4–6 ml/min/1.73 m^2 higher in both belatacept groups, though no P value was provided. It is hard to draw conclusions from this study given the small sample size and inadequate power.

The use of belatacept in high immunological risk patients was evaluated in a single-center study by Gupta et al. [65]. The study included six high immunological risk patients with history of re-transplantation, cPRA >83%, positive pre-transplant flow cross match, or prior ABMR. Patients were switched from TAC to belatacept due to evidence of acute calcineurin inhibitor (CNI) toxicity or interstitial fibrosis and tubular atrophy (IFTA) on biopsy. Renal function improved in all patients from a baseline mean eGFR of 23.8 ± 12.9 ml/min/1.73 m^2 to 42 ± 12.5 ml/min/1.73 m^2 including two patients who came off dialysis. There were no new episodes of acute rejection or evidence of subclinical rejection on follow-up protocol biopsies.

Switching to belatacept from a CNI-based therapy was further explored in a prospective randomized clinical trial. Rostaing et al. randomized 173 patients who were ≥6 months post-transplant but ≤36 months to remain on CNI-based regimen (44% CsA and 56% TAC) or switch to belatacept [66]. Patients had stable graft function with eGFR of 35–75 ml/min/1.73m^2. At 12 months, the mean eGFR increased in the belatacept group compared to the CNI-continuation group (mean eGFR 60.5 vs 56.5 ml/min/1.73m^2; $P = 0.0058$). The improvement in eGFR was most impressive in patients with baseline eGFR of 45–60 ml/min/1.73m^2. There was more acute rejection in the belatacept group (6 vs 0), but patient, graft survival, and safety profile were similar across groups. Another retrospective study evaluated the effect of switching to belatacept in patients with advanced graft dysfunction due to CNI toxicity. Seventy-nine kidney transplant patients with evidence of CNI toxicity and baseline mean eGFR of 26.1 ± 15.0 ml/min/1.73m^2 were converted from CNI based (50.6% TAC, 21.5% CsA) or mTOR inhibitor (mTORi)-based therapy to belatacept [67]. Mean eGFR improved to 34 ± 15.2 ml/min/1.73 m2 at 12 months. In patients with baseline eGFR of <25 ml/min/1.73 m^2, mean baseline eGFR was 17.2 ± 15.1 ml/min/1.73m^2 and improved to 27.3 ± 13.1 ml/min/m^2 ($P = <0.0001$) at 12 months.

In summary, in low immunological risk patients, belatacept-based maintenance immunotherapy appears to allow avoidance of CsA with comparatively better long-term renal function at the expense of increased risk for early acute rejection. It is less clear what the benefit is over a TAC-based regimen. Induction with Thymoglobulin or short-term concomitant use of TAC with belatacept might help to abate the risk for acute rejection. There is no strong data yet to support the use of belatacept in patients at high immunological risk (highly sensitized, prolonged cold ischemia time, older donor, re-transplant). These patients are probably better served by being on TAC/MMF-based therapy for the current time. Conversion to belatacept-based therapy in patients with suspected CNI toxicity also appears to be a reasonable and effective strategy. However, conversion should be considered early, before significant deterioration in graft function takes place.

Conclusion

In the changing and expanding landscape of transplantation, there is a need for large, well-designed, randomized clinical trials evaluating the variable induction and maintenance regimens. However, these studies are unlikely to be performed. Thus, experience-based practice continues to dominate. What is known is (1) lymphocyte depletion reduces the incidence of acute rejection in highly sensitized patients without clear evidence for improved long-term graft or patient survival, (2) post-transplant malignancy and viral infection risks are dictated by the overall degree of immunosuppression and choice of viral prophylaxis, (3) no strong evidence suggests significant benefit of alemtuzumab compared to Thymoglobulin as a lymphocyte depleting agent, (4) further studies are needed regarding the best concomitant induction agent to be used with belatacept, and (5) individualized immunosuppressive therapy based on patient's characteristics and immunological risk is important for successful transplantation.

Compliance with Ethical Standards

Conflict of Interest The primary author and all involved coauthors of this article have no financial or non-financial conflict of interest to declare. The manuscript is original and is currently not under consideration by any other journal and has not been published before.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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