

# Anti-interleukin-2 receptor antibodies—basiliximab and daclizumab—for the prevention of acute rejection in renal transplantation

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**Abstract:** The use of antibody induction after kidney transplantation has increased from 25% to 63% in the past decade and roughly one half of the induction agent used is anti-interleukin-2 receptor antibody (IL-2RA, ie, basiliximab or daclizumab). When combined with calcineurin inhibitor (CNI)-based immunosuppression, IL-2RAs have been shown to reduce the incidence of acute rejection, one of the predictors of poor graft survival, without increasing risks of infections and malignancies in kidney transplantation. For low-immunological-risk patients, IL-2RAs, as compared with lymphocyte-depleting antibodies, are equally efficacious and have better safety profiles. For high-risk patients, however, IL-2RAs may be inferior to lymphocyte-depleting antibodies for the prophylaxis of acute rejection. In an effort to reduce toxicities of other immunosuppressive medications without increasing the risk of acute rejection and chronic graft loss, IL-2RAs have often been combined with steroid- and CNI-sparing immunosuppression protocols. More data support the benefits of early steroid withdrawal with IL-2RA in low-risk patients, but preferred induction therapy for high-risk patients has yet to be determined. Although CNI-sparing protocols with IL-2RA may preserve renal function and improve long-term survival in selected patients, further studies are needed to identify those who benefit most from this strategy.

**Keywords:** basiliximab, daclizumab, interleukin-2 receptor antagonist, kidney transplantation, monoclonal antibody

## Introduction

Acute rejection episodes are one of the risk factors of developing chronic allograft injury and significantly reduce the long-term survival rates.<sup>1-3</sup> New and more potent immunosuppressive medications have reduced incidence of acute rejection and improved short-term graft survival, but they have not greatly enhanced long-term outcomes. One of the reasons for this observation may be the adverse effects of immunosuppressive medication that may contribute to graft dysfunction as well as mortality and morbidity of transplant patients; eg, calcineurin inhibitors (CNIs) cause acute and chronic nephrotoxicity and corticosteroids increase cardiovascular and other risk factors.<sup>4,5</sup> Immunosuppression agents can also be associated with infections and malignancies, which affect long-term patient survival.<sup>6</sup>

Because interleukin-2 (IL-2) plays a critical role in T-cell activation and proliferation, antibodies against  $\alpha$  subunit (CD25) of IL-2 receptor (IL-2R) have been tested in animal and human models.<sup>7-9</sup> Murine monoclonal antibodies to CD25 significantly reduce acute rejection episodes, but the high immunogenicity and short half-life of these antibodies limited their clinical use.<sup>7,10</sup> To overcome these problems,

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chimeric (basiliximab) and humanized (daclizumab) murine antibodies to CD25 have been developed. These agents have a high affinity and specificity for CD25 on the surface of activated T-cells and inhibit IL-2-mediated activation and proliferation of T-cells in transplant patients, aiming at a low acute rejection rate without affecting the pre-existing immune responses.

In this article we review the studies using anti-IL-2R antibody (IL-2RA) induction in renal transplantation, emphasizing the prevention of acute rejection in different protocols. We also examined the efficacy and safety of IL-2RA in combination with a reduction or avoidance of corticosteroids and CNIs, and compared IL-2RAs with lymphocyte-depleting monoclonal and polyclonal antibodies for induction therapy. Studies using IL-2RA for treatment of established rejection episodes are not included in this review.

## Dosage regimens and pharmacological properties

In phase III studies, two doses of basiliximab (20 mg each) were given on day 0 and day 4,<sup>11,12</sup> which saturates IL-2R $\alpha$  on the circulating lymphocytes for 4–6 weeks. Because of poor correlations between body weight and distribution volume or clearance, weight-adjusted dosing is not recommended for basiliximab.<sup>13,14</sup> Dosage modification is required for pediatric patients weighing <35 kg, who should receive two doses of 10 mg each.<sup>15</sup> On the contrary, phase III studies of daclizumab was conducted with a bodyweight-adjusted dose: 1 mg/kg once every two weeks for a total of five doses with cyclosporine (CsA)-based triple<sup>16</sup> or dual<sup>17</sup> maintenance immunosuppression; this suppresses IL-2R for up to four months after renal transplantation.<sup>16</sup> Subsequently, limited doses regimens (mainly two doses, at the time of transplant and 10–14 days thereafter) were tested with concomitant use of more potent baseline immunosuppression (eg, tacrolimus [TAC] and/or mycophenolate mofetil [MMF]).<sup>18–21</sup> Two doses of daclizumab were shown to be sufficient to block IL-2R $\alpha$  for more than 10 weeks.<sup>19</sup> A smaller study demonstrated one dose (2 mg/kg on day 0) and two doses (2 mg/kg on day 0 and 1 mg/kg on day 14) of daclizumab saturates the IL-2R $\alpha$  on the circulating lymphocytes for up to 42 days and 70 days, respectively.<sup>20</sup>

Because 90% of daclizumab and 75% of basiliximab are human immunoglobulin G (IgG), pharmacokinetic parameters are similar to exogenous human IgG antibodies. Both basiliximab and daclizumab have a small volume

distribution in the central component (2.5–5.0 L), and exhibit a low total body clearance (10–40 mL/hr). Unlike murine monoclonal antibodies, both chimeric and humanized antibodies have prolonged serum half-lives, seven days for basiliximab and 20 days for daclizumab, in adult renal transplant patients.<sup>13–16,20,22,23</sup> Limited data suggest drug interaction and pharmacokinetic alteration with CsA, TAC, azathioprine, and MMF.<sup>24–26</sup> Anti-idiotypic antibody development against the murine portion of these antibodies are rare owing to low immunogenicity.<sup>22,27</sup>

## IL-2RA with CsA-based dual or triple therapy

Following phase I/II studies by Amlot and Kovarik and colleagues,<sup>13,27</sup> the clinical efficacy and safety of basiliximab induction were evaluated with baseline immunosuppression consisting of cyclosporine microemulsion (CsA-ME) and steroids in two randomized, double-blind, placebo-controlled multicenter phase III trials.<sup>11,12</sup> International Study Group (Europe/Canada) demonstrated significant reduction of clinical and biopsy-proven acute rejection (BPAR) six months after deceased donor kidney transplantation (34% vs 52%,  $P < 0.001$  and 30% vs 44%,  $P = 0.012$ , respectively).<sup>11</sup> The incidence of steroid-resistant first rejection episodes that required antibody therapy was also significantly lower in the basiliximab group (10% vs 23%,  $P < 0.001$ ). The incidence of infection and other adverse events was similar in the two treatment groups. The acute tolerability of basiliximab was excellent, with no evidence of cytokine-release syndrome. A US trial of living or deceased donor kidney transplantation complied with these findings, showing significant reduction of rejection episodes: 38% vs 55% ( $P = 0.001$ ) for clinical rejection and 35% vs 49% ( $P = 0.009$ ) for BPAR at 12 months.<sup>12</sup> The rates of infection and other adverse events were similar. In both trials, the amount of steroids required was significantly lower in patients treated with basiliximab than in patients treated with placebo (0.56 vs 0.93 mg/kg/day,  $P < 0.001$ <sup>11</sup> and 0.59 vs 0.78 mg/kg/day,  $P = 0.02$ ,<sup>12</sup> both at four weeks post-transplant). Of note, only the US trial demonstrated better renal function at 1–12 months in patients treated with basiliximab. Patient and graft survival rates were not significantly different although the studies were not powered to detect small differences. In a pooled analysis of these two phase III trials, not only a significant reduction of acute rejection (by 44%,  $P < 0.01$ ) but also superior graft survival (96% vs 85%,  $P = 0.022$ ) were evident in diabetic subpopulation at one-year post-transplant with comparable safety profile.<sup>28</sup>

Combination of basiliximab and triple maintenance therapy (CsA-ME/ azathioprine/ steroids) was also evaluated in a randomized multicenter study.<sup>29</sup> During the first six months post-transplant, clinical acute rejection and BPAR occurred in 21%/19% of patients given basiliximab vs 35%/29% of patients administered placebo ( $P = 0.005$ ). Basiliximab, however, did not decrease the severity of rejection or rate of steroid-resistant rejection. The incidence of infections including cytomegalovirus (CMV) infections and other side effects were indistinguishable between patients given basiliximab and placebo. One-year patient and graft survival was similar in two groups.

Vincenti and colleagues reported the first clinical trial of daclizumab with excellent tolerability and safety,<sup>22</sup> which prompted two phase III, randomized, placebo-controlled clinical trials.<sup>16,17</sup> There were a total of 535 recipients of first deceased donor renal transplants randomized to receive five doses of daclizumab or placebo. In the first study, 126 daclizumab-treated recipients and 134 placebo-treated recipients received CsA, azathioprine, and steroids.<sup>16</sup> The second study was otherwise identical (daclizumab = 116 patients, and placebo = 111 patients), but concurrent immunosuppression consisted of only CsA and steroids (dual therapy).<sup>17</sup> In both studies, the addition of daclizumab significantly reduced the rate of BPAR (primary efficacy end-point) as compared with the placebo. At six months, the BPAR rate in patients treated with daclizumab was 22% vs 35% in those given placebo with triple therapy ( $P = 0.03$ ),<sup>16</sup> and 28% vs 47% with dual therapy ( $P = 0.001$ ).<sup>17</sup> The graft survival rates after one year tended to be higher in daclizumab-treated recipients in the first study (95% vs 90%,  $P = 0.08$ ). The second study demonstrated better patient survival (99% vs 94%,  $P = 0.01$ ), although the patient and graft survival of placebo patients in this study seemed to be lower than placebo patients in other phase III trials evaluating IL-2RA.<sup>17</sup> The graft function was also better in daclizumab-treated patients (58 vs 51 mL/min,  $P = 0.02$ ). Daclizumab was not associated with a higher incidence of infectious complications or cancers. Pooled analyses of these two studies demonstrated less frequent BPAR at one-year in daclizumab-treated patients as compared with placebo-treated patients (28% vs 43%,  $P < 0.01$ , 36% reduction by daclizumab).<sup>30,31</sup> This was not accompanied by improved graft survival at three years (84% vs 83% for triple therapy and 82% vs 78% for dual therapy), while the trials were inadequately powered to detect differences. The pooled three-year patient survival rate in the dual- and triple-therapy trials was 93% in daclizumab- and 91% in placebo-treated patients (not significant [NS]). The incidence of malignancies

or post-transplant lymphoproliferative disorder at three years in daclizumab and placebo patients was comparable in both clinical trials.

A meta-analysis of IL-2RA, including anti-Tac (murine IgG2a IL-2RA), BT563 (murine IgG1 IL-2RA), basiliximab, and daclizumab, has reported that treatment with IL-2RA was associated with a significant reduction in the risk of acute rejection at six months (odds ratio [OR] 0.51; 95% confidence interval [CI]: 0.42 to 0.63;  $P < 0.0001$ ).<sup>32</sup> The effect on acute rejection was similar for different types of IL-2RA: basiliximab (OR 0.56, 95% CI: 0.44 to 0.72;  $P < 0.0001$ ) and daclizumab (OR 0.46, 95% CI: 0.32 to 0.67;  $P < 0.0001$ ). The test for heterogeneity between antibody groups was not significant ( $P = 0.7$ ). The reduction in acute rejection was also similar for triple and dual immunosuppression regimens. There were no significant differences in the rate of graft loss, mortality, incidence of infections, or risk of malignancies at one year.

In summary, adding basiliximab or daclizumab to CsA-based dual or triple therapy reduces incidence of acute rejection without significant increase in infection or malignancy, although these initial trials evaluated IL-2RAs mainly on low-immunological-risk patients. The effect of IL-2RA on graft and patient survival was not fully validated and waits further evaluation.

## IL-2RA with MMF and/or TAC

In concert with the introduction of newer and more potent maintenance immunosuppressive medication, basiliximab and daclizumab were evaluated in different immunosuppressive protocols.<sup>26,33–38</sup> In a short report of a blind randomized trial, 75 patients treated with maintenance immunosuppression consisting of CsA, MMF, and steroids were administered daclizumab or placebo.<sup>39</sup> There was a six-month BPAR rate of 12% in daclizumab-treated patients as compared with 20% in those receiving placebo. The combination of daclizumab and maintenance triple therapy with MMF was safe, well tolerated, and demonstrated low incidence of acute rejection. In another nonrandomized trial evaluating the combination of daclizumab with MMF/steroids/CNI (CsA-ME or TAC), Iverson and colleagues compared 58 patients (64% Hispanic) who received living donor renal allografts with a matched cohort of 27 patients.<sup>33</sup> The four-month BPAR rate was 7% in daclizumab-treated patients vs 15% in control patients. There were no differences in the rate of adverse events, graft, and patient survival.

Lawen and colleagues randomized low-to-standard risk kidney transplant recipients to basiliximab ( $n = 59$ ) and

placebo ( $n = 64$ ) in addition to CsA-ME, MMF, and steroids in a multicenter, double-blind, placebo-controlled study.<sup>40</sup> Tolerability of basiliximab (the primary end point) was equivalent to placebo, with no increase in serious adverse events, infection, malignancy, or post-transplant lymphoproliferative disorder. At six months, while not powered to demonstrate a statistical significance, there were trends in favor of basiliximab over placebo in the incidence of first BPAR (15% vs 27%,  $P = 0.18$ ) and of acute rejection treated with antibody (5% vs 16%,  $P = 0.08$ ). There was also a trend to lower delayed graft function (DGF) and to improve graft function more rapidly in the basiliximab group than in the placebo-treated group.

A meta-analysis from the Cochrane Library included 117 reports from 38 randomized trials utilizing IL-2RA in renal transplantation.<sup>41</sup> Of those trials, 17 compared IL-2RA (10 basiliximab, 4 daclizumab, and 3 others) with placebo or no treatment, whereas 15 compared IL-2RA (9 basiliximab, 3 daclizumab, and 3 others) with other induction therapy (11 polyclonal antilymphocyte/thymocyte antibodies and 4 muromonab CD3). The majority of trials used CsA (31 CsA and 7 TAC) and MMF (23 MMF and 16 azathioprine). Acute rejection was significantly reduced at six months (relative risk [RR], 0.66, 95% CI: 0.59–0.74) and 12 months (RR, 0.67, 95% CI: 0.60–0.75) when IL-2RAs were compared with placebo. Graft loss, death, CMV infection, malignancy, and DGF all favored the use of IL-2RA, but none reached statistical significance because of lack of power. When added to standard dual or triple therapy, IL-2RA reduced the risk of clinically diagnosed acute rejection by 34% and the risk of steroid-resistant rejection by 49% as compared with non-induction therapy.<sup>41</sup>

TAC and MMF are often combined with more practical and cost-effective limited doses of daclizumab induction as opposed to the recommended five-dose regimen.<sup>18–20</sup> A multicenter study utilizing two doses of daclizumab on day 0 and day 10 post-transplant in 40 adult renal transplant recipients, in combination with TAC and MMF, demonstrated a BPAR rate of 13% during a median follow-up period of 29 weeks.<sup>19</sup> Ahsan and colleagues reported a prospective study comparing a single intraoperative dose of daclizumab (2 mg/kg,  $n = 50$ ) vs noninduction ( $n = 50$ ) in first low-immunological-risk kidney transplant patients treated with TAC, MMF, and prednisone.<sup>18</sup> During the first six months, episodes of first BPAR were 3/50 (6%) in the limited daclizumab group and 8/50 (16%) in the control group ( $P < 0.05$ ). Twelve-month patient and graft survival were not statistically different (100% vs 98% and 100% vs 94%,

respectively). These studies suggest that a limited dose of daclizumab when combined with a CNI, MMF, and steroids are sufficient for patients at low immunological risk to reduce early renal allograft rejection without adverse effects, and without the need for a more prolonged course of daclizumab as originally recommended.

## IL-2RA in high-immunological-risk patients

While majority of patients enrolled in randomized trials has low-to-standard immunological risk, IL-2RAs have been used with MMF and either CsA or TAC to reduce acute rejection in high-immunological-risk patients (Table 1).<sup>42–45</sup> Meier-Kriesche reported 29 black and 20 Hispanic renal transplant recipients treated with daclizumab (1 mg/kg  $\times$  five doses), CsA, MMF, and steroids, and compared with simultaneous cohort of 31 black and 25 Hispanic patients receiving the same immunosuppression without daclizumab induction therapy.<sup>44</sup> Acute rejection rates were lower in the daclizumab group than in the control group (26% vs 49% per patient years, respectively). A total of eight recurrent rejections in six patients occurred in the control group and none in the daclizumab arm. In another single center study, Ciancio and colleagues compared racial differences in incidence of BPAR among black ( $n = 37$ ), Hispanic ( $n = 85$ ), and Caucasian ( $n = 111$ ) first renal transplant recipients using daclizumab (1 mg/kg  $\times$  five doses), TAC, MMF, and steroids.<sup>42</sup> BPAR rate at one-year was 8.1% in black, 4.7% in Hispanic, and 4.5% in the Caucasian group ( $P = 0.7$ ). Graft and patient survival as well as renal function were comparable. Ciancio and colleagues also reported the use of daclizumab with TAC, MMF, and steroids in renal transplant recipients with previous transplants: 4 previous liver, 15 previous kidney, and 3 previous pancreas/kidney.<sup>46</sup> The incidence of BPAR was 0%, 13%, and 0% for previous liver, kidney, pancreas/kidney recipients, respectively. Few complications have occurred without CMV infection. These studies demonstrated the efficacy and safety of combining daclizumab, CNI, MMF, and steroids in high-immunological-risk patients.

## IL-2RA in CNI-sparing protocols

Because CNIs have intrinsic acute and chronic nephrotoxicity, IL-2RAs have been assessed for the potential addition to CNI-avoidance or -withdrawal after kidney transplantation (Table 2). The goal of this strategy is to maintain adequate renal function without increasing incidence of acute rejection.

**Table I** Immunological risk status

Population risk status	Race	Transplant type	PRA	HLA mismatch	Donor type	CIT	DGF
Low	Caucasian	Primary	PRA < 10%	0	Living related donor	< 18 hours	No
Standard							
High	Black	Repeat transplant with immunological loss of a previous allograft	PRA > 80%	6	Expanded criteria donor Donor after cardiac death (Deceased donor)	>36 hours	Yes

**Notes:** Patients are often categorized as “low risk” or “high risk” when some of the above criteria are met; “standard risk” are in between “high risk” and “low risk”, but actual definition may vary in each study.

**Abbreviations:** CIT, cold ischemia time; DGF, delayed graft function; HLA, human leukocyte antigen; PRA: panel reactive antibody.

## CNI avoidance and withdrawal

Two noncomparative studies reported complete avoidance of CNIs from the immunosuppressive protocol. In a multicenter trial reported by Vincenti and colleagues, 98 recipients of primary deceased or living donor kidneys at low immunological risk received daclizumab (2 mg/kg for the first dose and 1 mg/kg for the subsequent four doses), MMF (3 g/day for the first six months and 2 g/day thereafter), and corticosteroids.<sup>47</sup> BPAR was diagnosed in 48% of patients during the first six months and in 53% by 12 months after transplantation. At one-year post-transplant, 62% of patients had received CNI for more than seven days, predominantly because of rejection.

In a single-center study, Tran and colleagues used the similar protocol for 45 renal transplant recipients including 12 black patients.<sup>48</sup> The incidence of BPAR was 31% and occurred early in deceased donor transplant (median, 7 days); 51% of the patients required the addition of CsA maintenance. Although these studies provided benefits to a sizable minority of patients who have not required chronic CNI therapy with better renal function, the long-term results remain to be evaluated considering high incidence of acute rejection using this strategy.

The Cyclosporine Avoidance Eliminates Serious Adverse Renal-toxicity (CAESAR) trial compared CsA withdrawal (n = 179) and low-dose CsA (n = 183) with standard-dose CsA (n = 173) in low-immunological-risk recipients, all in combination with MMF (2 g/day) and steroids, but only withdrawal and minimization groups received daclizumab induction (2 mg/kg before transplant followed by four more doses of 1 mg/kg).<sup>49</sup> The primary end point of the study (renal function at 12 months) was not statistically different (glomerular filtration ratio [GFR] 51 mL/min/1.73 m<sup>2</sup> in CsA withdrawal group and low-dose CsA group, and 49 mL/min/1.73 m<sup>2</sup> in standard-dose CsA group). By withdrawing CsA at six months

after transplant, the patients experienced higher incidence of BPAR, as compared with low-dose CsA and standard-dose CsA patients (38% vs 25% vs 28%, respectively, *P* < 0.05). From this large-scale trial, it may be concluded that low-dose CsA is better than total withdrawal of CsA when combined with daclizumab induction, MMF, and steroids.

## CNI sparing with mTOR inhibitors

IL-2RA has also been combined with long-term use of mammalian target of rapamycin (mTOR) inhibitors (sirolimus [SRL] or everolimus) in lieu of CNIs or in addition to low-dose CNIs. Flechner and colleagues reported five-year outcomes of 61 low-to-standard risk patients randomized to SRL (target trough level 10–12 ng/ml for six months and 5–10 ng/ml thereafter) or CsA (target trough level 200 ng/ml for one year and 150–170 ng/ml thereafter) after basiliximab induction and MMF with steroids.<sup>50,51</sup> SRL-treated patients compared with CsA-treated patients demonstrated similar patient survival (87% vs 90%) and acute rejection rates (13% vs 23%), respectively. In SRL-treated patients, death-censored graft survival rate was higher (96% vs 77%, *P* = 0.027) and GFR was higher (67 vs 51 mL/min, *P* = 0.008) with similar urine protein and serum cholesterol levels. Martinez-Mier and colleagues used a similar protocol for 41 living related kidney transplants in a single center randomized trial, showing comparable patient and graft survival.<sup>52</sup> Although the rejection rate was numerically high in SRL-treated patients (17% vs 5%, NS), none of the patients who had target SRL levels suffered acute rejection at one year.

The Efficacy Limiting Toxicity Elimination (ELITE)-Symphony study is a prospective, randomized, open-label, multicenter trial comparing four parallel groups of adult renal transplant recipients.<sup>53</sup> Low-immunological-risk patients were randomly assigned to standard-dose CsA

Table 2 CNI-sparing clinical trials with IL-2RA induction therapy in kidney transplantation

Reference	No. of pts	Risk status	Induction	CNI or alternatives	Concomitant IS	BP/AR	Graft survival	Patient survival	Comments
Vincenti et al <sup>47</sup>	98	Primary Tx PRA < 20% (4% black, 23% LD)	Daclizumab	No CNI (Single arm)	MMF/CS	48% at 6 month 53% at 1 year	96% at 1 year	97% at 1 year	62% received CNI at 1 year
Tran et al <sup>48</sup>	45	(Mean PRA 5%, 27% black, 42% LD)	Daclizumab	No CNI (Single arm)	MMF/CS	31% with median f/u 8 mo	95%	100%	51% required CsA
Ekberg et al <sup>49</sup>	179	PRA < 20%	Daclizumab	CsA w/d at 6 month		38% (P < 0.05)	93% (NS)	96% (NS)	51 GFR at 1 year
CAESAR Study	183 173	(2% black, 23% LD)	Daclizumab None	Low-dose CsA Std-dose CsA	MMF/CS	25% 28% at 1 year	97% 95% at 1 year	97% 95% at 1 year	51 (NS) 49 ml/min/1.73 m <sup>2</sup>
Flechner et al <sup>50,51</sup>	31	Primary Tx (90% PRA < 10%, 25% black, 34% LD)	Basiliximab	SRL	MMF/CS	7% at 2 year 13% at 5 year	96% (P = 0.03)	87% (P = 0.68)	67 GFR at 5 year (P = 0.008)
	30	25% black, 34% LD)	Basiliximab	CsA	MMF/CS	17% at 2 year 23% at 5 year	80% at 5 year	90% at 5 year	51 ml/min
Martinez-Mier et al <sup>52</sup>	20	LD (related)	Basiliximab*	SRL	MMF/CS	17% (NS)	90% (NS)	100% (NS)	73 GFR at 1 year
	21	(Mexican)	CsA	CsA		5%	90%	100%	68 ml/min (NS)
Ekberg et al <sup>53</sup>	390	1st/2nd Tx <sup>†</sup>	None	Std-dose CsA		26% (P < 0.001)	92% (P = 0.007)	97% (P = 0.60)	57 (P < 0.001)
ELITE- Symphony Study	399 401 399	PRA < 20% (80% PRA = 0%, 2% black, 36% LD)	Daclizumab Daclizumab Daclizumab	Low-dose CsA Low-dose TAC Low-dose SRL	MMF/CS	24% (P < 0.001) 12% Reference 37% (P < 0.001) at 1 year	94% (P = 0.18) 96% Reference 92% (P = 0.007) at 1 year	98% (P = 0.35) 97% Reference 97% (P = 0.78) at 1 year	59 (P = 0.001) 65 Reference 57 (P < 0.001) GFR at 1 year (ml/min)
Nashan et al <sup>54</sup>	53	Primary Tx PRA < 80% (88% PRA = 0%, 21% black, 20% LD)	Basiliximab	Std-dose CsA		15% at 6 month 17% at 1 year	87%	91%	Efficacy failure 36% vs 17% at 3 year (P = 0.032)
	58		Basiliximab	Low-dose CsA	Everolimus/CS	19% at 3 year 3% at 6 month 7% at 1 year 12% at 3 year	97% at 3 year	97% at 3 year	Creatinine clearance 54 vs 61 ml/min at 1 year (P = 0.007)
Vitko et al <sup>55</sup>	112	Primary Tx (89% PRA < 10%, all black 6%)	None	Std-dose CsA	Low-dose everolimus	25% at 6 month 26% at 1 year	95%	99%	64 GFR at 1 year (P = 0.19)
Tedesco-Silva et al <sup>56</sup>	125	received Std-dose everolimus, 32% LD)	None	Std-dose CsA	Std-dose everolimus	15% at 6 month 19% at 1 year	97% at 1 year	95% at 1 year	63 (NS)
A2306 study	117		Basiliximab	Low-dose CsA	Low-dose everolimus	14% at 6 month 14% at 1 year	98%	100%	68
A2307 study	139		Basiliximab	Low-dose CsA	Std-dose everolimus	15% at 6 month 16% at 1 year	95% at 1 year	99% at 1 year	68 ml/min

Vincenti et al <sup>100</sup> Belatacept study	74	High-risk (Re-Tx, PRA > 20%) < 10% (98% PRA < 20%, 8% black, 27% LD)	Basiliximab Intensive belatacept	7%	96%	99%	66 GFR at 1 year ( $P = 0.01$ )
	71		Basiliximab Less-intensive belatacept	6%	99%	100%	62 ( $P = 0.04$ )
	73		Basiliximab Std-dose CsA	8% at 6 month	97% at 1 year	95% at 1 year	54 mL/min/1.73 m <sup>2</sup>

**Abbreviations:** BPAR, biopsy-proven acute rejection; CNJ, calcineurin inhibitor; CS, corticosteroids; CsA, cyclosporine A; GFR, glomerular filtration ratio; IS, immunosuppression; LD, living donor; MMF, mycophenolate mofetil; NS, not significant; PRA, panel reactive antibody level; SRL, sirolimus; Std, standard; TAC, tacrolimus; Tx, transplant.

**Notes:** \*Only for patients with more than three HLA mismatch; †Excluding immunological graft loss within 12 months after the first transplant.

( $n = 390$ , target trough level, 150–300 ng/ml for three months and 100–200 ng/ml thereafter), low-dose CsA ( $n = 399$ , target trough level, 50–100 ng/ml), low-dose TAC ( $n = 401$ , target trough level, 3–7 ng/ml), or low-dose SRL ( $n = 399$ , target trough level, 4–8 ng/ml). All groups received MMF (2 g/day) and corticosteroids. Daclizumab (2 mg/kg before transplant followed by four more doses of 1 mg/kg) was given to all but the standard-dose CsA group. Estimated GFR at one year (the primary end point) was significantly higher in the low-dose TAC group (65 mL/min) than in the other three groups (57–59 mL/min,  $P < 0.001$ ). BPAR rate at one year was lower in the low-dose TAC group (12.3%) than in the other three groups (standard-dose CsA 25.8%, low-dose CsA 24.0%, low-dose SRL 37.2%;  $P < 0.001$ ). Death-censored allograft survival was higher in the low-dose TAC group (96%) than in the standard-dose CsA and the low-dose SRL groups (both 92%;  $P = 0.007$ ). Serious adverse events were observed in 53% of patients in the low-dose SRL group, as compared with 43%–44% in the other groups ( $P < 0.05$ ). Based on the results above, when daclizumab is combined with low-dose TAC, outcomes seem to be better than standard CsA-MMF-steroid-based regimen without induction therapy; however, when daclizumab is combined with low-dose SRL without CNIs, outcomes seem to be worse than the standard triple regimen.

Low-dose CNI with mTOR inhibitor has been tested in other studies. Nashan and colleagues compared full-dose CsA ( $n = 53$ , trough level, 125–250 ng/ml) and reduced-dose CsA ( $n = 58$ , trough level, 50–100 ng/ml) in combination with basiliximab, everolimus (3 mg/day) and steroids in a randomized, multicenter, open-label study (156 study) of low-to-standard risk patients.<sup>54</sup> In the reduced-dose CsA group, a lower incidence of BPAR (3% vs 15% at six months and 7% vs 17% at one year) was accompanied by higher mean creatinine clearance (61 vs 54 mL/min at one year,  $P < 0.007$ ) and less frequent discontinuations and serious adverse events. Vitko and colleagues and Tedesco-Silva and colleagues reported six- and 12-months safety and efficacy results of two randomized studies (A2306 and A2307) of low-to-standard risk patients using the similar immunosuppressive medication.<sup>55,56</sup> Study 1 (A2306,  $n = 237$ ) had no induction therapy; in Study 2 (A2307,  $n = 256$ ) basiliximab was administered. These studies compared two different doses of everolimus (1.5 vs 3 mg/day) with steroids and reduced-dose CsA (initial CsA C<sub>2</sub> target 1200 ng/ml for Study 1 and 600 ng/ml for Study 2 with subsequent tapering to 400 ng/ml for both studies). As black patients have a higher everolimus clearance rate than Caucasian patients, all black

subjects received 3 mg/day everolimus. These regimens were well tolerated and preserved renal function throughout the study, with no differences observed between groups within studies. Without basiliximab induction, there was a trend towards a reduction in the incidence of BPAR among nonblack randomized to 3 mg/day everolimus as compared with 1.5 mg/day everolimus (16% and 26% at 12 months, respectively;  $P = 0.08$ ). The inclusion of basiliximab lowered the overall incidence of acute rejection (15% for 3 mg/dl and 14% for 1.5 mg/dl at six months; 16% vs 14% at 12 months).

## Delayed CNI introduction

As designed in phase I/II studies, the other potential use of IL-2RA induction is to delay introduction of CNIs to prevent acute nephrotoxicity while the transplanted kidney has delayed or slow graft function.<sup>13</sup> Small studies reported initial CNI avoidance with a combination of daclizumab/basiliximab, SRL, and steroids. This regimen provided reasonable acute rejection prophylaxis in 43 kidney recipients (acute rejection rate 16%).<sup>57</sup> In a retrospective analysis of 14 patients, Chang and colleagues added MMF to this regimen, resulting in an acute rejection rate of 14% and graft survival rate of 100% during the follow-up period of 0.5–5.2 months.<sup>37</sup> Although SRL may prolong recovery from DGF,<sup>58</sup> the ability of IL-2RA to protect kidneys from acute rejection with excellent safety profile makes this strategy attractive. Moreover, it has been suggested that use of an IL-2RA may decrease the risk of delayed or slow graft function.<sup>12,59,60</sup>

The French Myeariade FR01 study group evaluated early and delayed CsA in a 12-month, prospective, randomized, open-label study of *de novo* low-risk renal transplant patients.<sup>61,62</sup> CsA-ME at an initial dose of 8 mg/kg/dose was started either on day 0 ( $n = 97$ ) or day 6 ( $n = 100$ ) post-transplant, and dose adjusted according to  $C_2$  level. All patients received enteric-coated mycophenolate sodium, steroids, and either two doses of basiliximab or five doses of daclizumab. One-third of patients in both groups had a DGF Risk Index Score of  $\geq 5$  (US Renal Data System). The incidence of BPAR was numerically high (26% vs 16%;  $P = 0.11$ ) at 12 months in the delayed CsA-ME group as compared with the early CsA-ME group, although the study was not powered to detect differences. Early or delayed introduction of CsA-ME did not affect renal function (51 ml/min vs 54 ml/min at three months;  $P = 0.43$ ) or DGF rate (27% vs 23%; NS). The extension of this study with a mean follow up of 30 months demonstrated comparable

creatinine clearance between groups. NI2A Study Group in Spain also compared different patterns of CsA initiation in renal transplant recipient from expanded criteria donors and high risk of DGF: early low-dose CsA (3 mg/kg/day,  $n = 38$ ), early standard-dose CsA (5 mg/kg/day,  $n = 40$ ), and delayed standard-dose CsA (5 mg/kg/day 7–10 days after transplant,  $n = 36$ ).<sup>63</sup> This multicenter six-month, open-label, randomized trial with basiliximab, MMF, and steroids revealed no differences among groups in six months GFR, DGF rate (31%, 38%, and 42% for early low-dose CsA, early standard-dose CsA, delayed standard-dose CsA, respectively), and BPAR rate (5%, 13%, and 11%), although combined clinically treated and BPAR rate was significantly higher in the delayed CsA group (5%, 15%, and 25%). These results suggest delayed introduction of CNIs with IL-2RA, MMF, and steroids does not improve renal function or lower DGF rate; it may increase acute rejection episodes.

In summary, results of CNI sparing protocols have been mixed. Minimization of CNIs may be associated with improved renal function; however, CNI avoidance or withdrawal often increases risk of acute rejection. Further study is needed to determine whether the short-term benefit of CNI minimization translates into long-term improvement of graft and patient survival with alternative immunosuppressive medication including IL-2RA induction and mTOR inhibitors.

## IL-2RA in corticosteroid sparing protocols

Corticosteroids have been a mainstay of immunosuppression for several decades despite their major adverse effects: hypertension, diabetes, dyslipidemia, bone loss, avascular necrosis, weight gain, cataracts, and psychotic behavior. Although these side effects may increase mortality and morbidity after transplantation, steroid withdrawal has been associated with high rejection rate and poor graft survival.<sup>64–67</sup> To prevent rejection early post-transplant, antibody induction including IL-2RA has been utilized in steroid-sparing protocols (Table 3).

## Steroid withdrawal with CNIs and MMF

A pilot study by Cole and colleagues introduced daclizumab and MMF to a CsA-based immunosuppressive protocol to avoid steroid use. Sixty-five percent of patients remained steroid-free with acute rejection rate of 25%, suggesting this as a practical strategy.<sup>68</sup> Vincenti and colleagues randomized 84 low-to-standard risk primary renal transplant recipients receiving basiliximab, CsA-ME, and MMF to

either corticosteroid withdrawal at day 4 post-transplant or standard steroid therapy.<sup>69</sup> The incidence of BPAR at 12 months was comparable (20% vs 16%;  $P = 0.73$ ) with 100% death-censored graft survival in both groups. The majority (72%) of patients remained off steroids, showing feasibility of steroid-withdrawal with basiliximab.

With TAC and MMF-based immunosuppression, ter Meulen and colleagues randomized low-to-high risk patients to three-day steroids plus two doses of daclizumab (daclizumab group,  $n = 186$ ) and four-month steroids (control group,  $n = 178$ ).<sup>21</sup> The incidence of BPAR at 12 months (15% vs 14%) and graft survival (91% vs 90%) were comparable between the daclizumab and control groups. Mean arterial blood pressure, serum lipids, and incidence of patients with hyperglycemia were temporarily lower in the daclizumab group than controls. The efficacy of daclizumab was also tested in the CARMEN study: an open-label, multicenter, parallel-group study with 538 low-to-standard risk renal patients randomized to a daclizumab/TAC/MMF or a TAC/MMF/corticosteroids.<sup>70</sup> The patients who received two doses of daclizumab and no steroids demonstrated the same low BPAR rate (17% in both groups) as compared with controls. The steroid-free patients were found to have reduced incidence of insulin-dependent new-onset diabetes after transplantation (0.4% vs 5.4%;  $P = 0.003$ ), lower total cholesterol level, and similar renal function. These results suggest daclizumab is as effective at preventing acute rejection after renal transplantation as a standard triple regimen and its safety benefits may help improve the long-term outcome of renal transplant patients.

Parrott and colleagues tested the effectiveness of basiliximab in avoiding addition of steroids to CsA-ME monotherapy.<sup>60</sup> In the low-to-standard immunological risk patients randomized to receive basiliximab ( $n = 52$ ) or placebo ( $n = 56$ ), more placebo-treated patients (73%) required additional immunosuppression at 12 months than basiliximab-treated patients (54%,  $P = 0.05$ ). BPAR episodes were observed more frequently in placebo (43%) than in basiliximab (29%) although it was not statistically significant ( $P = 0.16$ ). These findings suggest the efficacy of basiliximab as compared with placebo in steroid-sparing regimens. However, in the Atlas Study, Vitko and colleagues reported higher incidence of BPAR in steroid-free patients at low-to-standard immunological risk.<sup>71</sup> Two steroid-free regimens (TAC monotherapy after basiliximab induction and TAC/MMF) had BPAR rate of 26% and 31%, respectively, as compared with standard triple therapy (TAC/MMF/steroids) of 8% ( $P < 0.001$ ). Graft and patient survival were similar

in all groups as was the renal function at six months. The basiliximab/TAC therapy offered some safety benefits (fewer events of leucopenia, diarrhea, and CMV infection).

Woodle and colleagues for the Astellas Corticosteroid Withdrawal Study Group recently published five-year results of a prospective, randomized, double-blind, placebo-controlled multicenter trial comparing seven-day corticosteroid cessation versus long-term, low-dose corticosteroid therapy.<sup>72</sup> About one-third of the patients at low risk in each group received either basiliximab or daclizumab, while two-thirds of patients received antithymocyte globulin. Overall, there was no difference in a composite outcome of death, graft loss, or moderate/severe acute rejection (16% and 14% in steroid withdrawal group and chronic steroid group, respectively). The BPAR rate at five years was numerically higher (18% vs 11%;  $P = 0.06$ ) and the Kaplan–Meier analysis of BPAR was significantly higher in the steroid withdrawal group ( $P = 0.04$ ) primarily because of mild, Banff 1A, steroid-sensitive rejection. Of note, subgroup analysis revealed similarly low incidence of BPAR with chronic steroid use in patients induced with antithymocyte globulin (10%) and IL-2RA (12%); the incidence of BPAR was numerically higher with IL-2RA (24%) than antithymocyte globulin (14%,  $P = 0.09$ ) in steroid-withdrawal patients. Corticosteroid withdrawal was associated with improved serum triglycerides, less body weight change, and fewer insulin-dependent new-onset diabetes after transplant.

Another recently published trial using basiliximab is the FREEDOM study, which compared complete steroid avoidance and seven-day steroid withdrawal with standard chronic steroid therapy.<sup>73</sup> Vincenti and colleagues randomized 336 low-risk renal patients into three treatment groups with CsA-ME, enteric-coated mycophenolate sodium, and basiliximab. The 12-month incidence of BPAR, graft loss, or death of the intent-to-treat population was 36% in the steroid-free group ( $P < 0.01$  vs standard), 30% in steroid withdrawal (NS vs standard) and 19% in standard steroids. BPAR was significantly more frequent with steroid free and steroid withdrawal than standard steroids (steroid free 32%,  $P < 0.01$ ; steroid withdrawal 26%,  $P = 0.05$ ; standard steroids 15%). GFR at 12 months was similar and investigational groups were not inferior to standard steroids in the observed-case analysis. Favorable outcomes in new-onset diabetes after transplant, dyslipidemia, and weight gain were observed in one or both steroid-minimization groups versus standard steroids. These results suggest steroid withdrawal at one week is more desirable than steroid avoidance

**Table 3** Steroid-sparing clinical trials with IL-2RA induction therapy in kidney transplantation

Reference	No. of pts	Risk status	Induction	Corticosteroids	Concomitant IS	BPAR	Graft survival	Patient survival	Comments
Cole et al <sup>68</sup>	57	Primary Tx (98% PRA < 10%, 2% black, 51% LD)	Daclizumab	No CS (Single arm)	CsA/MMF	19% at 1 year	89% at 1 year	95% at 1 year	65% remained CS-free
Vincenti et al <sup>69</sup>	43	Primary Tx	Basiliximab	CS w/d at day 4	CsA/MMF	20% (P = 0.73)	100%	100%	72% remained
	40	PRA < 50% (8% black, 50% LD)	Basiliximab	Std CS		16% at 1 year	100%	98%	CS-free
Ter Meulen et al <sup>71</sup>	186	1st/2nd Tx	Daclizumab	CS w/d at day 3	TAC/MMF	15%	91%	95%	
	178	(78% PRA < 10%, 10% PRA > 50%, 4% black, 36% LD)	None	CS w/d in 4 mo		14% at 1 year	90% at 1 year	94% at 1 year	
Rostaing et al <sup>70</sup>	260	Primary/Re-Tx*	Daclizumab	No CS	TAC/MMF	17%	92% (P = 0.06)	98% (P = 0.43)	0.4% NODAT
CARMEN study	278	PRA < 50% (Caucasian)	None	Std CS		17% at 6 month	96% at 6 month	99% at 6 month	5.4% (P = 0.003)
Parrott et al <sup>60</sup>	52	1st/2nd Tx	Basiliximab	No CS	CsA (mono)	29% (P = 0.16)	88% (NS)	98% (NS)	54% IS addition
	56	(3% PRA > 50%, 96% white, 22% LD)	Placebo	No CS		43% at 1 year	88% at 1 year	96% at 1 year	73% (P = 0.046)
Vitko et al <sup>71</sup>	153	Primary Tx	Basiliximab	CS w/d at day 1	TAC (mono)	26% (P = 0.001)	95% (NS)	99% (NS)	1% NODAT
ATLAS study	151	PRA < 50% (Caucasian, 12% LD)	None	CS w/d at day 1	TAC/MMF	31%	97%	99%	7%
	147		None	Std CS	TAC/MMF	8% at 6 month	96% at 6 month	100% at 6 month	5% (P = 0.06)
Woodle et al <sup>72</sup>	191	Primary/Re-Tx <sup>†</sup>	Basiliximab or Daclizumab or Thymoglobulin	CS w/d at day 7	TAC/MMF	18% (P = 0.06)	94% (P = 0.36)	94% (P = 0.78)	NODAT (insulin)
Astellas study	195	PRA < 25% (20% black, 57% LD)		Std CS		11% at 5 year	96% at 5 year	93% at 5 year	22% (4%) vs 21% (12%) (P = 0.05 for insulin)
Vincenti et al <sup>73</sup>	112	Primary Tx, PRA < 20%	Basiliximab	No CS CS w/d at day	CsA/EC-MPS	32% (P = 0.004)	96% (NS)	95% (NS)	Less body weight gain, dyslipidemia, and NODAT in CS-spring
FREEDOM study	115	(3% black, 40% LD)	Basiliximab	7		26% (P = 0.046)	98% (NS)	98% (NS)	
	109		Basiliximab	Std CS		15% at 1 year	97% at 1 year	98% at 1 year	
Woodle et al <sup>75</sup>	77	Primary TX PRA < 50% Nonblack (74% LD)	Basiliximab	CS w/d at day 4 (Single arm)	TAC/SRL	13% at 1 year	100% at 1 year	100% at 1 year	
Anil Kumar et al <sup>76</sup>	75	PRA < 10% (60% black, 22% LD)	Basiliximab	CS w/d at day 2	TAC/MMF	12%	90% (NS)	95% (NS)	22% mod/severe CAN
	75		Basiliximab	CS w/d at day 2	TAC/SRL	8%	90% at 2 year	97% at 2 year	10% (P = 0.06)
Kumar et al <sup>77</sup>	150	PRA < 10% (54% black, 14% LD)	Basiliximab	CS w/d at day 2	TAC/MMF or TAC/SRL	16%	78%	91%	Subclinical rejection and CAN (NS)
	150		Basiliximab	Std CS		14% at 3 year	79% at 3 year	89% at 3 year	NODAT 4% vs 21% (P < 0.01)

Gallon et al <sup>78</sup>	45 37	(0% ReTx, 3% PRA > 25%, 24% black, 70% LD)	Basiliximab Basiliximab	CS w/d at day 2 CS w/d at day 2	TAC/MMF TAC/SRL	18% ( $P = 0.31$ ) 30%	98% ( $P = 0.04$ ) 84% at 3 year	100% ( $P = 0.43$ ) 98% at 3 year	GFR better in TAC/MMF
Montagnino et al <sup>79</sup>	65 68	1st/2nd Tx PRA < 50% (Italian, 6% LD)	Basiliximab Basiliximab	CS w/d at day 7 Std CS	CsA/everolimus	32% ( $P = 0.06$ ) 18%	95% (NS) 87% at 3 year	100% 97% at 3 year	46% resumed CS

**Abbreviations:** BPAR, biopsy-proven acute rejection; CAN, chronic allograft nephropathy; CNL, calcineurin inhibitor; CS, corticosteroids; CsA, cyclosporine A; GFR, glomerular filtration ratio; IS, immunosuppression; MMF, mycophenolate mofetil; EC-MPS, enteric-coated mycophenolate sodium; NODAT, new-onset diabetes after transplantation; NS, not significant; SRL, sirolimus; Std, standard; TAC, tacrolimus; w/d, withdrawal.

**Notes:** \*Excluding immunological graft loss within 12 months after the previous transplant; †Excluding nontechnical graft loss of previous transplant. Patients with delayed/slow graft function or acute rejection within seven days post-transplant were also excluded.

for standard-risk renal recipients receiving basiliximab, CsA-ME, and enteric-coated mycophenolate sodium.

Pascual and colleagues recently published meta-analysis of steroid avoidance or withdrawal for kidney transplant recipients in the Cochrane Library.<sup>74</sup> Overall, acute rejection was more frequent with a steroid-sparing strategy analyzing intent-to-treat population (RR 1.27, 95% CI: 1.14–1.40), or only biopsy-proven cases (RR 1.59, 95% CI: 1.21–2.11), although none of the steroid withdrawal (>2 weeks post-transplant) studies and only about a half of the steroid avoidance (<2 weeks post-transplant) studies analyzed were induced by IL-2RA. Steroid withdrawal showed no effect on death, graft loss, or acute rejection; whereas steroid avoidance showed no effect on death or graft loss, but more frequent acute rejection as compared with steroid use and maintenance. In a subgroup analysis stratified by the type of CNI (CsA and TAC), higher incidence of acute rejection was only evident in studies using CsA. A meta-analysis comparing with or without induction, or comparing the type of induction was not performed.

## Steroid withdrawal with CNIs and mTOR inhibitors

IL-2RA induction has been used with mTOR inhibitor-based immunosuppression to minimize steroid use. Woodle and colleagues combined basiliximab, TAC, and SRL in a single arm multicenter pilot study.<sup>75</sup> Low-risk renal recipients were withdrawn from steroids four days after transplantation and demonstrated excellent one-year patient and graft survival (both 100%). BPAR occurred in 13% and presumptive rejection 11%, with good renal function and safety profile. Anil Kumar and colleagues compared SRL and MMF (n = 75 each) in combination with basiliximab, TAC, and two-day steroid (60% black recipients) with surveillance biopsy at 1, 6, 12, and 24 months post-transplant.<sup>76</sup> BPAR was seen in 12% of TAC/MMF and 8% of TAC/SRL patients. Surveillance biopsy showed that cumulative incidence of subclinical acute rejection was 27% in TAC/MMF and 16% in TAC/SRL groups at two years ( $P = 0.04$ ), and that moderate/severe chronic allograft nephropathy was 22% and 10%, respectively ( $P = 0.06$ ). Two-year patient and graft survival were equivalent. A comparison of steroid withdrawal and standard steroids of the same investigators showed no increase in BPAR, subclinical acute rejection, or chronic allograft nephropathy; and low incidence of new-onset diabetes after transplant (4% vs 21%,  $P < 0.01$ ) in the steroid withdrawal group.<sup>77</sup> In contrast to above studies, Gallon and colleagues reported a single-center analysis of

low-to-standard risk renal recipients comparing TAC/MMF ( $n = 45$ ) and TAC/SRL ( $n = 37$ ) with basiliximab plus two-day steroids.<sup>78</sup> During the three-year follow-up, graft survival was significantly better in TAC/MMF group (98%) than in TAC/SRL group (84%,  $P = 0.04$ ). Numerically fewer patients experienced BPAR in TAC/MMF (8/45, 18% vs 11/37, 30%,  $P = 0.31$ ). Of note, 70% of the rejection occurred within 30 days post-transplant in both group, suggesting inadequate initial protection by basiliximab.

Utilizing another mTOR inhibitor, Montagnino and colleagues randomized 133 *de novo* renal transplant recipients at low-to-standard risk to seven-day steroid withdrawal and low-dose chronic steroids with basiliximab, low-dose CsA-ME, and everolimus.<sup>79</sup> There were more BPAR in steroids withdrawal group (21/65, 32%) than in the low-dose steroid group (12/68, 18%,  $P = 0.06$ ). Graft survival was paradoxically high in steroid withdrawal group (95% vs 87%, NS) but only 54% of the patients were steroid-free at three years after transplant: 17 resumed steroids because of acute rejection and 13 were never withdrawn from steroids because of slow graft function. Larger randomized studies are needed to confirm these results and clarify the benefits of steroid withdrawal in CsA-mTOR inhibitor-based immunosuppression.

## Steroid withdrawal in high-immunological-risk patients

In high-immunological-risk patients, Alloway and colleagues withdrew steroids from TAC (target trough level, 4–8 ng/ml), SRL (target trough level, 8–12 ng/ml), and MMF (2 g/day).<sup>80</sup> Although initial 10 patients received daclizumab induction (2 mg/kg on days 0 and 14), the protocol for the next 15 patients was modified, because of high acute rejection rate, to receive antithymocyte globulin (1.5 mg/kg on days 0 and 2) followed by daclizumab on day 14. Of 25 patients, 40% were black, 68% repeated transplant, and 36% had peak flow PRA > 25%. The incidence of acute rejection was 60% with daclizumab and 27% with antithymocyte globulin plus daclizumab. Anil Kumar and colleagues evaluated the safety and efficacy of steroid withdrawal at day 2 post-transplant in black ( $n = 103$ ) as compared with nonblack ( $n = 103$ ) kidney recipients.<sup>81</sup> Induction was basiliximab and maintenance was CNI (TAC target trough level, 15–18 ng/ml or CsA target C2 level, 1000–1200 ng/ml) plus MMF (2 g/day) or SRL (target trough level, 5–10 ng/ml). Although BPAR rates at one-year were similar (16% for black and 13% for nonblack), the incidence of subclinical acute rejection at one month was higher in the black group than the nonblack group (23% vs 11%;  $P = 0.04$ ). A five-year follow-up of

the study demonstrated still a significant difference of subclinical acute rejection but no difference in clinical BPAR (16% vs 14%,  $P = 1.0$ ).<sup>82</sup> Five-year patient survivals were 81% and 88% ( $P = 0.09$ ) and graft survivals were 71% and 73% ( $P = 0.19$ ) in the black and nonblack groups, respectively. Prevalence of chronic allograft injury (48% vs 30%;  $P = 0.05$ ), interstitial fibrosis/tubular atrophy (47% vs 32%;  $P = 0.05$ ), and mean serum creatinine levels (2.1 vs 1.8 mg/dl;  $P = 0.05$ ) were all higher in the black group.

In summary, early steroid withdrawal in low-to-standard immunological risk patients with IL-2RA induction and CNI-based maintenance therapy is possible with minimal increasing risk of rejection and is probably better than total avoidance of steroids. Steroid-sparing may decrease incidence and severity of steroid-related adverse events; however, long-term benefits of this strategy have not yet been proven.

## Comparison of IL-2RA and other antibodies Basiliximab vs daclizumab

No large-scale randomized study has directly compared two different IL-2RAs. Nair and colleagues reported a small open-labeled prospective study of 23 renal transplant recipients comparing the efficacy of basiliximab (20 mg on day 0 and day 4) and daclizumab (1 mg/kg for five doses) with baseline immunosuppression of CsA, MMF, and steroids.<sup>83</sup> There was no significant difference in the rate of acute rejection, 10% with basiliximab and 8% with daclizumab; time to first rejection episode was eight days with basiliximab versus six weeks with daclizumab. There was no difference in patient and graft survival (100%) between the two groups at 10 months follow-up. Lin and colleagues randomized 30 patients to basiliximab and 28 patients to daclizumab with CsA, reduced-dose MMF (1 g/day), and steroids.<sup>84</sup> At six months, the incidence of BPAR was 0% with basiliximab and 21% with daclizumab ( $P < 0.05$ ). However, relatively low-dose daclizumab (fixed dose of 50 mg on days 0 and 14) was used in this study as compared with other two-dose regimen studies using total dose of 4 mg/kg.<sup>85,86</sup> Two meta-analyses of randomized trials utilizing IL-2RA in kidney transplantation demonstrated a similar effect on acute rejection for basiliximab and daclizumab: OR 0.56 vs 0.46 in the first study and RR 0.67 vs 0.66 in the second study.<sup>32,41</sup>

## IL-2RA vs muromonab CD3

Ciancio and colleagues retrospectively compared first kidney transplant patients with daclizumab induction ( $n = 233$ ) and

muromonab CD3 (OKT3) induction ( $n = 225$ ).<sup>87</sup> Daclizumab was administered in standard five doses (1 mg/kg every other week) and muromonab CD3 7–14 doses (5 mg daily) with delayed (2–3 days) TAC, MMF, and steroids. At six months, the BPAR rate was significantly lower in daclizumab-treated patients (2%) than in muromonab CD3-treated patients (7%,  $P = 0.01$ ). One-year patient and graft survival for the daclizumab group was 98% and 96% vs 96% and 94% for the muromonab CD3 group, respectively (NS). The incidence of infection requiring hospitalization was lower with daclizumab (7 vs 16%;  $P < 0.004$ ) with a similar trend with CMV infection (2% vs 4%;  $P = 0.14$ ). In an updated report of additional recipients ( $n = 305$ ), the efficacy and safety of daclizumab was still observed: BPAR rate of 5% with median follow-up of 27 months and CMV infection in 1.6% of the patients.<sup>88</sup> The median length of hospital stay was shorter in the basiliximab group than the muromonab CD3 group (10 vs 13 days;  $P = 0.0001$ ). A similar observation was reported by Kode and colleagues.<sup>89</sup> In a single-center study, 100 standard-to-high immunological risk patients who received a first or second kidney graft from deceased donor were treated with two doses of basiliximab, low-dose CsA, MMF, and reduced-dose steroids. A historical control group consisted of 26 patients who received muromonab CD3 (7–14 daily doses), delayed full-dose CsA, MMF, and high-dose steroids. Despite a 40% reduction in steroids, basiliximab-treated patients had fewer BPAR (basiliximab 14% vs muromonab CD3 35%) and required less antilymphocyte antibody therapy. Length-of-stay, number of readmissions, total hospitalization days, and CMV infections were lower in the basiliximab group.

## IL-2RA vs antithymocyte globulin

Sollinger and colleagues compared the safety and efficacy of basiliximab ( $n = 70$ ) and equine antithymocyte globulin (ATGAM;  $n = 65$ ) with CsA-ME, MMF, and steroids in low-to-standard risk patients.<sup>90</sup> At 12 months, the rate of BPAR was 19% and 20%, respectively, in the basiliximab and antithymocyte globulin groups; graft survival, patient survival, and adverse event profile were similar. Lebranchu and colleagues compared basiliximab plus early CsA-ME ( $n = 50$ ) versus rabbit antithymocyte globulin (Thymoglobulin®) plus delayed CsA-ME ( $n = 50$ ) in low-risk, first, deceased-donor kidney transplant patients; all patients received MMF and steroids.<sup>91</sup> The incidences of BPAR (8% in each group) and treatment failure (14% in the basiliximab group vs 8% in the antithymocyte globulin group) were comparable in the two groups. There was a tendency to more

DGF requiring dialysis (14% vs 6%) and significantly fewer CMV infections (12% vs 38%;  $P = 0.005$ ) in the basiliximab group. Another small comparison of low-risk renal patients receiving daclizumab ( $n = 10$ ) and antithymocyte globulin (Fresenius,  $n = 35$ ) indicated comparable efficacy and fewer infectious complications in the daclizumab group.<sup>92</sup> Kyllonen and colleagues reported five-year results of a single-center study randomizing standard-risk patients to single bolus antithymocyte globulin (Fresenius, 9 mg/kg over 30 min before reperfusion), basiliximab (20 mg before reperfusion and on day 4), and no induction.<sup>93</sup> All patients received CsA, azathioprine, and steroids, but CsA blood trough level was significantly high in no induction group during the first week post-transplant. BPAR rate was numerically low in two induction groups compared with no induction group (antithymocyte globulin 11%, basiliximab 12%, and no induction 21%, NS). Antithymocyte globulin was associated with lower incidence of DGF (6%, 24%, and 16%;  $P < 0.03$ ) and higher incidence of adverse events during infusion (ie, low blood pressure, high airway pressure, and low oxygen saturation). Patient and graft survival was similar at five years except that basiliximab group had higher graft survival than no induction group (97% vs 84%;  $P < 0.05$ ). In terms of long-term adverse events including CMV infection, there were no statistically significant differences among the three groups.

Two recent open-label, multicenter, randomized studies compared basiliximab and rabbit antithymocyte globulin (Thymoglobulin®). Mourad and colleagues randomized 105 low-risk renal transplant patients to basiliximab and antithymocyte globulin with delayed CsA-ME, MMF, and steroids.<sup>94</sup> The incidence of BPAR was comparable (basiliximab 10% vs antithymocyte globulin 9%) as were the graft survival (94% vs 96%), patient survival (98% for both studies), DGF rate (29% vs 30%), and renal function (mean serum creatinine nadir 163 vs 156  $\mu\text{mol/L}$ ). However, significantly fewer patients in the basiliximab group experienced CMV infection, leukopenia, and thrombocytopenia, and this was without any significant difference in any other key safety parameters (including the incidence of serum sickness, fever, lymphoma, and infections in general). Brennan and colleagues reported an international study comparing a short course of antithymocyte globulin (Thymoglobulin® 1.5 mg/kg intraoperatively and four more daily doses,  $n = 141$ ) and basiliximab (20 mg on days 0 and 4,  $n = 137$ ) in patients at high risk for acute rejection or DGF who received a deceased-donor renal transplantation.<sup>95,96</sup> Both groups received CsA-ME, MMF, and steroids for maintenance immunosuppression.

The antithymocyte globulin group, as compared with the basiliximab group, had lower incidences of BPAR (16% vs 26%,  $P=0.02$  at one year) and antibody-treated BPAR (1.4% vs 8%;  $P=0.005$  at one year). The antithymocyte globulin group and basiliximab group had similar incidence of DGF (40% vs 45%), graft survival (91% vs 90% at one year, 69% vs 63% at five years) and patient survival (96% vs 96% at one year, 76% vs 80% at five years). The incidence of all adverse events, serious adverse events, and cancers were also similar between the two groups at one year. The patients receiving basiliximab had a lower incidence of infection (86% vs 75%;  $P=0.03$  at one year); contrary to other studies, the incidence of CMV disease was higher in the basiliximab group (8% vs 18%;  $P=0.02$  at one year). These findings suggest that incidence of acute rejection is comparable with IL-2RA and antithymocyte globulin in kidney transplant recipients at low-immunological-risk, but the risk of rejection may be higher with IL-2RA in patients at high risk.

## IL-2RA vs alemtuzumab

Kaufman and colleagues reported a nonrandomized, retrospective sequential study comparing outcomes in kidney transplant recipients induced with either alemtuzumab ( $n=123$ ) or basiliximab ( $n=155$ ) in combination with a steroid-free maintenance protocol using TAC and MMF.<sup>97</sup> The one-year actual death-censored graft survival rates for recipients who received alemtuzumab and basiliximab were both 99%; the one-year actual patient survival rates were 97% vs 99% (NS). A lower rate of early (<3 months) rejection was observed in the alemtuzumab versus the basiliximab group (4% vs 12%, respectively), but the rates for both groups were equivalent at one year (15% and 14%). At one year, serum creatinine concentration was similar ( $1.42 \pm 0.59$  mg/ml for the alemtuzumab group and  $1.36 \pm 0.48$  mg/ml for the basiliximab group). The incidence and etiology of infectious disease were very similar: CMV infection occurred in 4% and 5% of the recipients in the alemtuzumab and basiliximab groups, respectively. The incidence of CMV in CMV-naïve recipients who received CMV-positive donor organ were 21% and 19% in the respective two groups. Authors concluded that alemtuzumab induction therapy was similar in efficacy to basiliximab in a steroid-free maintenance immunosuppressive protocol for kidney transplant recipients.

At our institution, Ciancio and colleagues randomized 90 first deceased-donor renal transplant recipients (>50% non-Caucasian) into three different antibody induction agents: group A received rabbit antithymocyte globulin, group B alemtuzumab, and group C daclizumab.<sup>98,99</sup> Maintenance

immunosuppression included TAC and MMF in all three arms, and corticosteroids in groups A and C only. The targeted trough TAC level was 8–10 ng/ml for groups A and C, with a targeted MMF dose of 1 g twice daily. In group B, target trough TAC level was 4–7 ng/ml (to reduce long-term nephrotoxicity), with 500 mg twice-daily doses of MMF and without corticosteroid maintenance. In a 15-month median postoperative interval report, there were no notable differences in demographics or patient and graft survival.<sup>98</sup> However, a following report with a minimum follow-up of 27 months showed significantly poorer death-censored graft survival in group B as compared with group A and C combined ( $P=0.01$ ).<sup>99</sup> BPAR rates at one year were equivalent, ie, 5 of 30 in all three groups (17%). Longer follow-up again showed equivalent BPAR rate, but higher incidence of chronic allograft nephropathy in group B (37%,  $P=0.008$ ) as compared with group A (17%) and group C (10%). In group B, there was slightly lower renal function throughout the observation. There was also significantly more leukopenia, but a greater percentage of T regulatory cells and number of Fox-P3 mRNA copies in group B. There were no differences in other adverse events. These results indicate that with the alemtuzumab induction, 80% of patients remain steroid-free two years postoperatively; however, they have higher incidence of immunological graft loss, chronic allograft nephropathy, and poor renal function. IL-2RA induction with conventional maintenance immunosuppression may be superior to alemtuzumab induction with low maintenance in a certain patient population.

## Combination of IL-2RA and other antibodies

Vincenti and colleagues randomized mainly low-risk patients receiving deceased or living donor kidney graft into three immunosuppressive regimens to test the efficacy of belatacept (selective costimulation blocker, binds CD80 and CD86 of antigen-presenting cells) without CNI maintenance.<sup>100</sup> Patients in the intensive belatacept group received belatacept 10 mg/kg  $\times$  11 doses in the first six months with subsequent 5 mg/kg doses every 4–8 weeks; patients in the less-intensive belatacept group received belatacept 10 mg/kg  $\times$  five doses in the first three months with subsequent 5 mg/kg doses every 4–8 weeks; and patients in the CsA group received CsA maintenance. All patients received induction therapy with 20 mg of basiliximab on days 0 and 4, 2 g of MMF daily, and a corticosteroid-tapering regimen to 5 mg per day. At six months, the incidence of BPAR was similar among the groups: 7% for intensive belatacept, 6% for less-intensive

belatacept, and 8% for CsA. At 12 months, the measured GFR was significantly higher among patients receiving the intensive and less-intensive belatacept regimens than among those receiving CsA (66, 62, and 54 ml/min/1.73 m<sup>2</sup>, respectively;  $P < 0.05$ ). Chronic allograft nephropathy was less common with both regimens of belatacept than with CsA (29%, 20%, and 44%, respectively). Overall, adverse event profiles are in favor of both belatacept regimens, suggesting potential long-term benefit of less toxic antibody therapy with IL-2RA and costimulation blockade.

Finally, Ciancio and colleagues combined truncated daclizumab (1 mg/kg  $\times$  2 doses on days 0 and 14) and short-course of rabbit antithymocyte globulin (1 mg/kg  $\times$  three doses on days 0, 3, and 5) along with reduced-dose TAC, early steroid withdrawal (one week), and either MMF or enteric-coated mycophenolate sodium for 150 first kidney transplant recipients consisting of 36% Caucasian, 30% Hispanic, and 29% black.<sup>101</sup> At 12 months, overall incidence of BPAR was 6% and BPAR requiring antibody treatment was 3%. One-year patient and graft survival was 99% and 96%, respectively. The percentage and types of infectious complications requiring hospitalization during the first 12 months post-transplant was acceptably low (14% for all infection, 0.7% for CMV infection). The incidence of new-onset diabetes mellitus after transplantation was 11%; gastrointestinal side effects were seen in 16% of the patients without significant difference by maintenance immunosuppressive regimen. This study demonstrates the efficacy and safety of combined induction therapy with IL-2R and lymphocyte-depleting antibody with low-dose CNI and rapid steroids elimination for an ethnically diverse population of renal transplant recipients.

## Conclusions

The use of antibody induction after kidney transplantation has increased from 25% to 63% in the past decade and roughly one half of the induction agent used is IL-2RA, ie, basiliximab or daclizumab.<sup>102</sup>

Evidence supports basiliximab and daclizumab, as compared with placebo, equally reduce incidence of acute rejection without significant increase in incidence and severity of adverse events. In many immunosuppressive combinations, efficacy of IL-2RA for low- and standard-immunological-risk patients is similar to that of lymphocyte-depleting antibodies and the safety profile is usually better than other antibody preparations.

Given the high safety and tolerability profile, IL-2RAs have successfully been used with steroid- and CNI-sparing

protocols in order to reduce toxicities of immunosuppressive medications. For low-to-standard risk patients, early steroid withdrawal with IL-2RA seems to be feasible with minimal, if at all, increasing risk of rejection when combined with CNI-based immunosuppressive regimens. In contrast, results of CNI-sparing protocols with IL-2RA have been mixed. CNI withdrawal may be associated with improved renal graft function and minority of patients may benefit from this strategy, CNI minimization, however, often increases risk of acute rejection. Further studies are needed to evaluate the overall benefits of these new strategies on the long-term survival of patients and allografts.

## Disclosures

The authors have no conflicts of interest that are directly relevant to the content of this review.

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