Transplant International ISSN 0934-0874

REVIEW

Interleukin-2 receptor antagonist induction in modern immunosuppression regimens for renal transplant recipients

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Keywords
basiliximab, daclizumab, interleukin-2, interleukin-2 receptor antagonist, rabbit antithymocyte globulin, thymoglobulin.

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Received: 5 December 2006
Revision requested: 26 January 2006
Accepted: 14 March 2006

doi:10.1111/j.1432-2277.2006.00321.x

Summary

Addition of interleukin-2 receptor antagonist (IL-2RA) induction to calcineurin inhibitor (CNI)-based regimens reduces biopsy-proven acute rejection by 30–40%. IL-2RA induction facilitates early withdrawal of steroids, and supports the safe use of reduced-exposure CNI or delayed CNI introduction. IL-2RAs and rabbit antithymocyte globulin (Thymoglobulin®) show comparable efficacy in patients at standard or low immunologic risk, but the adverse event profiles of lymphocyte-depleting agents are less favorable. IL-2RAs, uniquely, provide effective immunosuppression with similar tolerability to placebo.

Introduction

The interleukin-2 receptor antagonists (IL-2RAs) basiliximab and daclizumab have become widely adopted since their introduction in the mid-90s. Initially, IL-2RA agents were administered only as adjunctive immunosuppression within full-exposure calcineurin inhibitor (CNI)-based regimens. As experience has grown, however, clinicians have increasingly investigated the use of IL-2RAs in other protocols including steroid-sparing and CNI-sparing regimens. It is timely, therefore, to evaluate IL-2RA induction in a variety of clinical settings and to consider the relative roles of IL-2RA induction and lymphocyte-depleting agents. In April 2005, a panel of transplant specialists from Europe, North America and Japan convened in Madrid, Spain, to review the use of IL-2RA induction in renal transplantation in a range of contexts; a summary of their discussions is presented here. Evidence is graded

according to published standards [*Grade I*: evidence from ≥1 properly randomized, controlled trial; *Grade II*: evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments; *Grade III*: evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees] [1].

Biological effects of IL-2RA induction

Interleukin-2 receptor antagonists bind with high affinity to the α subunit of the IL-2 receptor (IL-2Rα or CD25), activating intracellular tyrosine kinases that inhibit T-cell cytokine production (Fig. 1). As the α subunit is expressed only on activated T-cells, resting T-cells remain unaffected, such that the IL-2 receptor is a highly specific target for biological intervention.

The high selectivity of IL-2RAs is simultaneously the reason for their excellent tolerability and the reason why an immune response may still be mounted in the presence of IL-2RA induction, by bypassing the IL-2 pathway. However, IL-2RAs may also modulate the immune response through an effect on receptors for other cytokines. Although the α subunit is unique to the IL-2 receptor, the IL-15 receptor includes the β subunit (Fig. 1), while both the IL-15 and IL-7 receptor contain the γ unit. IL-15 contributes to activation of antigen-presenting cells, and to the proliferation of T-cells and natural killer cells, as well as stimulating production of other cytokines such as IL-10 or interferon-γ. Flow cytometry analysis in 29 renal transplant patients has shown that during treatment with basiliximab, IL-7-dependent T-cell proliferation was not affected, but IL-15-dependent T-cell proliferation was inhibited, although to a lesser extent than IL-2-dependent proliferation (mean inhibition 20% vs. 62%) [2].

Development of tolerance to allografts appears to be unaffected by IL-2RAs. *In vitro* evidence indicates that IL-2RAs affect the function of donor-specific regulatory cells [3]. The moderate suppression of IL-15 by IL-2RA agents may be beneficial in this context, as IL-15 is essential for the homeostatic proliferation of memory CD8 T-cells, which is, in turn, believed to impair the development of tolerance to the allograft.

In summary, IL-2 is important for amplification of the immune response, and selective blockade of the IL-2Rα (CD25) subunit is a rational target for biological intervention. IL-2RAs block IL-2 binding to activated T-cells but resting T-cells remain unaffected. Selective blockade with an IL-2RA agent does not prevent other cytokines from activating T-cells, although there is some evidence that the effect of IL-15 may be partially muted because of down-regulation of the shared IL-2Rβ chain.

Efficacy of IL-2RA induction with standard immunosuppressive regimens

A series of multicenter, randomized, placebo-controlled studies with basiliximab and daclizumab in combination with cyclosporine (CsA) (using trough level monitoring) and steroids, with or without azathioprine, have consistently demonstrated a significant 30–40% relative reduction in the incidence of biopsy-proven acute rejection [4–8]. Four of these trials reported the incidence of steroid-resistant rejection compared with placebo; in three of

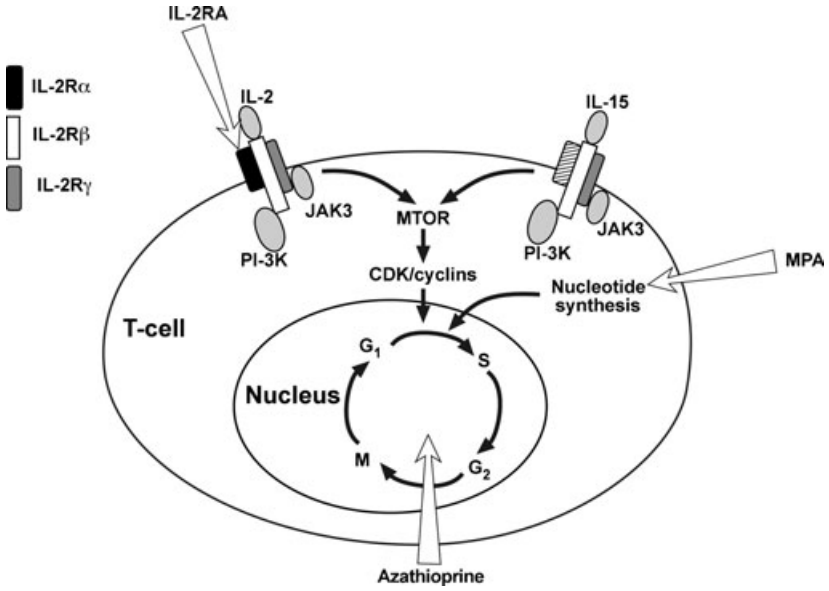

Figure 1 Mode of action of interleukin-2 (IL-2) receptor antagonists. IL-2RA, IL-2 receptor antagonist; MPA, mycophenolic acid; JAK3, Janus kinase 3; PI-3K, phosphoinositide-3-kinase; MTOR, molecular target of rapamycin; CDK, cyclin-dependent kinase.

these, the incidence was significantly lower with IL-2RA induction than placebo [4,5,7]. Two smaller trials have evaluated addition of IL-2RA induction to CsA, steroids and mycophenolate mofetil (MMF) [9,10]. These showed a relative reduction in acute rejection of 44% (15% vs. 27%, $n = 123$) [9] and 30% (14% vs. 20%, $n = 75$) [10], respectively, but were not powered to show a statistically significant difference. As a result, no definitive clinical data are available to support the use of IL-2RAs in a regimen including mycophenolic acid from time of transplant, and it should be determined on an individual basis whether the additional cost of IL-2RA induction is justified to prevent rejection in patients who can tolerate a full-dose triple regimen with mycophenolic acid. Randomized, comparative studies of IL-2RA induction versus no induction in patients receiving tacrolimus-based immunosuppression are lacking.

A meta-analysis has reported that the acute rejection rate was significantly lower with IL-2RA induction at 6 months (12 trials, relative risk 0.66) and at 1 year (10 trials, relative risk 0.67) versus placebo (Table 1) [11]. In the same analysis, the relative risk of graft loss at 1 year was 0.84, a difference that did not reach statistical significance (95% CI: 0.64–1.10); data from only four trials were available for 3-year graft survival rates (relative risk 1.08; 95% CI: 0.71–1.64). These findings were similar to those reported in a smaller meta-analysis (Table 1) [12].

In summary, addition of IL-2RA induction to dual therapy (CNI and corticosteroids) or triple therapy (CNI, steroids and azathioprine) results in a decrease in the relative risk of biopsy-proven acute rejection of 30–40%, and steroid-resistant acute rejection is also reduced (*Grade I*). Fewer studies have reported outcomes when IL-2RA induction is added to CNI-based regimens containing MMF; the two reported trials have shown a similar decrease in rejection rates, but were not powered to achieve significance (*Grade I*).

Dosage of IL-2RA induction agents

The licensed dosage of basiliximab is two 20-mg doses administered intravenously on the day of transplant and on day 4 after transplant, based on pharmacodynamic data indicating that this regimen provides 4–6-week CD25 suppression [13]. All randomized trials of basiliximab have adhered to this dosage schedule, and no comparative trials have been undertaken to compare this with alternative doses or administration times. For daclizumab, the dose is weight-adjusted. The daclizumab license stipulates five doses (1 mg/kg) given on the day of transplant and four times subsequently at 14 days apart, which inhibits CD25 for approximately 4 months [8]; this five-injection schedule was used in each randomized trial of daclizumab versus placebo. There are some limited data available concerning the use of modified daclizumab dosing schedules. A pharmacokinetic/pharmacodynamic study by Vincenti *et al.* [14] has shown that two 1 mg/kg daclizumab are associated with saturation of CD25 for 59 days. Interim data from a randomized study in simultaneous kidney–pancreas patients has reported the efficacy of two-dose daclizumab (2 mg/kg × 2) to be similar to that seen with the standard regimen (1 mg/kg × 5) [15], but data in renal transplant patients are limited [16,17]. A randomized study of 46 renal transplant patients has reported a similar 6-month incidence of acute rejection with basiliximab (6%) and two 1 mg/kg doses of daclizumab (7%) [18]. In contrast, Lin *et al.* [19] observed a significantly higher incidence of acute rejection at 6 months with two-dose daclizumab (days 1 and 14) versus two-dose basiliximab (21% vs. 0%, $P < 0.05$) in a randomized study of 58 *de novo* renal transplant patients. The relative effectiveness of modified regimens of daclizumab requires further examination in well-designed trials.

In a pilot study undertaken in a population of 57 pediatric patients, extended daclizumab therapy was administered to 6-month post-transplant (total dose 10 mg/kg) with tacrolimus and MMF but no steroids, and results compared against historical controls group [20]. Clinical acute rejection was 8% at 1 year in the daclizumab-treated patients and there was 98% graft and patient survival. Extended use of IL-2RA induction has not been reported by other authors.

IL-2RA induction and steroid minimization regimens

Avoiding long-term exposure to steroids has well-recognized advantages, including reduced risk of hypertension, diabetes, weight gain, osteopathy, peptic ulceration, cosmetic effects or, in children, growth impairment. Certain patient types may derive particular benefit from steroid minimization strategies, such as the elderly, children, obese patients, or those at increased risk of cardiovascular disease, diabetes, low bone mass or a history of gastric ulcers. In terms of suitability for steroid minimization regimens, most studies have focused on low immunologic risk individuals, but there is some evidence to suggest that African–American patients may be successfully managed with steroid minimization using IL-2RA induction [21].

Steroid withdrawal was initially attempted at 3–6-months post-transplant but, increasingly, more aggressive minimization strategies are being adopted whereby steroid therapy is withdrawn within the first week post-transplant in order to avoid development of steroid dependence and rebound rejection after late discontinuation. There is emerging evidence for clinical benefits of steroid with-

Table 1. Registry analyses and meta-analyses of interleukin-2 receptor antagonist (IL-2RA) induction.

Trial	Design	Inclusion criteria	*n*	Key findings
Webster *et al*. [11]	Meta-analysis	Randomized, controlled trials of IL-2RA induction versus placebo/control, versus other induction agents, or versus other IL-2RA induction agent (renal transplants)	38 trials $n = 4893$	Compared with placebo, IL-2RA induction is associated with: 1. Significantly reduced risk of acute rejection at 6 months (RR 0.66, 95% CI: 0.59–0.74) and 12 months (RR 0.67, 95% CI: 0.60–0.75) 2. No significant difference in graft loss (RR 0.84, 95% CI: 0.64–1.10) 3. No increase in cytomegalovirus (CMV) infection (RR 0.82, 95% CI: 0.65–1.03) 4. No increase in malignancy (RR 0.67, 95% CI: 0.33–1.36)
Adu *et al*. [12]	Meta-analysis	Randomized, controlled trials of IL-2RA induction versus placebo/control in CsA-treated (renal transplants)	8 trials $n = 1858$	Compared with placebo/control, IL-2RA induction is associated with: 1. Significantly reduced risk of acute rejection (OR 0.51, 95% CI: 0.42–0.63) 2. No significant difference in graft loss (OR 0.78, 95% CI: 0.58–1.04) 3. No significant difference in mortality (OR 0.75, 95% CI: 0.46–1.23) 4. No increase in incidence of infection (OR 0.97, 95% CI: 0.77–1.24) 5. No increase in risk of malignancy (OR 0.82, 95% CI: 0.39–1.70
Cherikh *et al*. [52]	Registry analysis (UNOS)	Primary renal transplants undertaken 1997–2000	$n = 38\,519$	Compared with no induction, increased risk of post-transplant lymphoproliferative disease was 29% with polyclonal induction ($P = 0.27$) and 14% with IL-2RA induction ($P = 0.52$). Compared with no induction, IL-2RA induction is associated with: 1. 17% reduced risk of graft loss ($P = 0.002$) 2. 21% reduced risk of mortality ($P = 0.005$)
Opelz *et al*. [51]	Registry analysis (CTS)	All types of solid organ transplant undertaken	$n = \sim 200\,000$	Use of IL-2RA induction was not associated with an increased risk of lymphoma

CTS, collaborative transplant study; OR, odds ratio; RR, relative risk; CI, confidence interval.

drawal during the first week post-transplant among patients receiving IL-2RA induction. In the CARMEN study, 538 patients were randomized to receive daclizumab and a single dose of steroids on the day of transplantation or a standard steroid regimen, both in combination with tacrolimus and MMF [22]. Patients given only single-dose steroids were significantly less likely to develop new-onset diabetes mellitus (defined as requirement for insulin >30 consecutive days in previously nondiabetic patients) by 6 months than those given standard steroid therapy (0.4% vs. 5.4%, $P = 0.003$) and mean total cholesterol decreased by 0.19 mmol/l in the daclizumab/single-dose steroids group compared with a rise of 0.19 mmol/l with standard steroid therapy ($P = 0.005$). A large, randomized trial undertaken in The Netherlands, in which patients again received tacrolimus and MMF, has also shown that early steroid withdrawal (day 4) with IL-2RA induction resulted in a significantly lower risk of new-onset diabetes and improved lipid profiles [23]. Other trials, all of which used CsA-based immunosuppression, have either not reported metabolic changes [24,25] or have shown a trend to improvement in the steroid-withdrawal patients [26].

Five trials using IL-2RAs have randomized patients to early steroid withdrawal (by day 7 post-transplant) or to standard steroid therapy, of which one (CARMEN) [22] used tacrolimus-based immunosuppression and the remainder used CsA therapy (Table 2). Of these, four found a similar incidence of biopsy-proven acute rejection in the steroid-withdrawal groups and control patients [22–24,26]. Preliminary results from the first multicenter, randomized, controlled three-arm study (FREEDOM) comparing steroid avoidance versus early steroid withdrawal (day 7) versus standard maintenance steroids are now available [25]. In this multicenter, open-label study of *de novo* renal transplant patients given basiliximab, enteric-coated mycophenolic acid and cyclosporine (C_2 monitoring), there was a significant increase in biopsy-

Table 2. Clinical trials of early steroid withdrawal with IL-2RA induction therapy in renal transplant recipients.

Trial	Design	*n*	Population risk status	Maintenance immuno-suppression	Steroid withdrawal group	Control group	BPAR (biopsy-proven acute rejection) at 1 year in steroid withdrawal group versus controls (% patients)	*P*	Steroid-free maintenance at 1 year (% patients in withdrawal group)
Rostaing *et al*. (CARMEN study) [22]	Multicenter randomized open label	538	Normal or high	Tacrolimus mycophenolate mofetil (MMF)	Daclizumab single dose of steroids (day 0)	No daclizumab standard steroid regimen	16.5% vs. 16.5%*	NS	89%*
ter Meulen *et al*. [23]	Multicenter randomized open label	364	Normal or high	Tacrolimus MMF	Daclizumab steroids stopped at day 4	No daclizumab steroids continued to week 16	15% vs. 14%	NS	Not available
Vincenti *et al*. [24]	Multicenter randomized open label	83	Normal	Cyclosporine MMF	Basiliximab steroids stopped at day 4	Basiliximab standard steroid regimen	20% vs. 16%	NS	72%
Vincenti *et al*. (FREEDOM study) [25]†	Multicenter randomized open label	175‡	Normal (immediate graft function)	CsA MMF	Basiliximab steroids stopped day 7	Basiliximab standard steroid regimen	15.6% vs. 5.9%§	NS	Not available
Kumar *et al*. [26]	Single-center randomized open label	77	Normal or high	CsA MMF	Basiliximab steroids stopped day 2	Basiliximab standard steroid regimen	16% vs. 13%	NS	Not available
Woodle *et al*. [27]	Multicenter single arm	77	Normal	Tacrolimus sirolimus	Basiliximab steroids stopped at day 4		23.5%	–	79%

*At 6-month post-transplant.
†Preliminary results.
‡Patients in the early steroid cessation and standard-steroids cohorts.
§At 3-month post-transplant.

proven acute rejection at 3 months in the steroid avoidance group (20.6% vs. 5.9% in the standard steroid group, $P = 0.006$) [19], while the group with early steroid withdrawal (by day 7) had a 15.6% rejection rate ($P = 0.052$ versus standard therapy). Generally, it appears that 65–90% of patients in whom steroids are withdrawn during the first week post-transplant can be maintained on a steroid-free regimen long term [22,24,27]. However, the duration of follow-up in all these studies was relatively short and longer-term data are required to determine efficacy and any benefits in terms of steroid-related adverse events.

Completely steroid-free regimens with IL-2RA induction have been assessed in two single-arm pilot studies [28,29]. In a multicenter Canadian study, 57 adult patients at low-to-moderate immunologic risk were treated with a regimen consisting of five doses of daclizumab, cyclosporine and MMF [28]. At 1 year, the incidence of biopsy-proven rejection was 25%. In a pediatric trial at Stanford University, 77 pediatric patients were treated with a steroid-free regimen consisting of extended daclizumab therapy (6 months), tacrolimus, and MMF. The incidence of biopsy-proven rejection at 1 year was 8%, and 1.2% beyond 1 year [29]. As noted above, preliminary results from the FREEDOM study showed that the 3-month rejection was significantly higher in patients randomized to receive no steroids versus those given a standard steroid regimen [25]. Twelve-month results will determine overall safety and efficacy. Recently, a nonrandomized trial of alemtuzumab versus basiliximab using a steroid-free regimen with tacrolimus and MMF has reported more encouraging rates of early rejection (alemtuzumab 4.1%, basiliximab 11.6% at 3 months post-transplant) [30], but these single-center data require validation. Overall, on the basis of current evidence, early steroid withdrawal within the first week post-transplant may be preferable to complete steroid avoidance.

In summary, large randomized, controlled trials have shown that, in a regimen including IL-2RA induction with CNI-based therapy, withdrawal of steroids within the first week post-transplant in standard-risk patients is possible without a significant increase in risk of rejection (*Grade I*). However, the long-term safety benefits of this steroid-sparing strategy have not yet been proven. Early results (to 3 months post-transplant) suggest that initial steroid administration (<1 week) with IL-2RA induction is advisable instead of complete steroid avoidance (*Grade II*).

IL-2RA induction and CNI minimization regimens

Several trials have assessed the use of CNI minimization strategies with IL-2RA induction, including low-exposure regimens, delayed introduction of CNI and complete CNI avoidance (Table 3) [31–41]. Although further data are required, IL-2RA induction appears to support low-exposure CNI therapy without loss of efficacy [31,36,37]; one large-scale randomized study reported a similar incidence of rejection with standard cyclosporine exposure or reduced exposure with IL-2RA induction [31]. Efficacy also appears to be maintained with reduced blood levels of cyclosporine in patients receiving a proliferation signal inhibitor (mTOR) and IL-2RA induction [32,33], although intracellular cyclosporine exposure may not have been reduced profoundly because of the interaction between cyclosporine and mTOR inhibitors.

Data supporting delay of CNI initiation are more limited [36,38–40]. A multicenter trial conducted in 197 patients receiving MMF and steroids has reported that cyclosporine introduction on day 6 is associated with a similar risk of rejection to immediate introduction when given with IL-2RA induction [35]. If CNI initiation is delayed beyond day 6, efficacy appears to be diminished even with use of IL-2RA induction [36,38].

Complete CNI avoidance in a regimen with IL-2RA induction, mycophenolic acid, and steroids is associated with an unacceptably high level of rejection although outcomes are good in those who remain rejection-free [41–43]. Adding sirolimus to such a regimen may improve the results: a combination of MMF, sirolimus and steroids has been assessed in two trials with similar protocols, except that one trial included basiliximab induction and the other did not [43,44]. Using basiliximab in a single-center trial, two out of the 31 patients (6.4%) receiving this regimen experienced biopsy-proven acute rejection at 1 year [43]. In the multicenter trial without IL-2RA induction, the incidence was 11 out of 40 CNI-free patients (27.5%) [44]. However, patient numbers were small: thus, these results require confirmation in a larger randomized, controlled, multicenter study.

Calcineurin inhibitor avoidance utilizing belatacept (LEA29Y; a second-generation CTLA4Ig in clinical development) with IL-2RA induction and MMF [45] has shown encouraging preliminary results.

As the available data are largely confined to low immunologic risk patients, CNI-free regimens, even with IL-2RA induction, should be restricted to patients at low immunologic risk in view of serious concerns about rejection in higher risk individuals.

In summary, IL-2RA induction may support use of reduced-exposure CNI without loss of efficacy (*Grade I*), but further data are required. CNI avoidance with IL-2RA induction, MMF, and steroids is associated with an increased risk of rejection (*Grade I*). One single-center study [43] supports the use of IL-2RAs with a CNI-free

Table 3. Clinical trials of calcineurin inhibitor (CNI) minimization with IL-2RA induction therapy in renal transplant recipients. Population size refers to total number of patients in the treatment group and the control group.

Trial	Design	Population size (*n*)	Population risk status	Maintenance immuno-suppression	CNI minimization group	Control group	BPAR at 1 year in CNI minimization group versus controls (% patients)	*P*	Renal function at 1 year in CNI minimization group versus controls	*P*
Low-exposure CNI										
Vincenti *et al.* [31]	Multicenter randomized open label	356*	Normal	MMF steroids	Daclizumab reduced exposure cyclosporine (CsA)	Standard CsA exposure	25% vs. 28%	NS	eGFR (estimated glomerular filtration rate) 72 ml/min vs. 66 ml/min	NS
Andres *et al.* [36]	Multicenter randomized open label	78	High risk of delayed graft function (DGF)	MMF steroids	Basiliximab CsA 3 mg/kg	Basiliximab CsA 5 mg/kg	5.3% vs. 15%†‡	NS	Serum creatinine (SCr) 179 μmol/l vs. 178 μmol/l‡	NS
Nashan *et al.* [32]	Multicenter randomized open label	111	Normal	Everolimus steroids	Basiliximab reduced CsA exposure	Basiliximab standard CsA exposure	6.9% vs. 17.0%	Not available	eGFR 61 ml/min vs. 54 ml/min	0.007
Boletis *et al.* [37]	Single-center historical controls	80	Normal	MMF steroids	Basiliximab CsA 3 mg/kg on day 4	Basiliximab CsA 6 mg/kg on day 0	0% vs. 0%	NS	eGFR 67 ml/min vs. 59 ml/min	<0.03
Vitko *et al.* [33]	Two multicenter studies (RAD 2306 and RAD 2306)§	256 (RAD 2306) 237 (RAD 2307)	Normal	Everolimus steroids	Basiliximab reduced CsA exposure weeks 1–8 (RAD 2307)	Basiliximab standard CsA exposure (RAD 2306)	14.5% vs. 19.8%‡	NS	eGFR 65 ml/min vs. 66 ml/min‡	NS
Delayed CNI introduction										
Mourad *et al.* [35]	Multicenter randomized open label	197	Normal or high	*myfortic* steroids	Basiliximab or daclizumab CsA on day 6	Basiliximab or daclizumab CsA on day 0	24% vs. 19%‡	NS	eGFR 49 ml/min vs. 53 ml/min†‡	NS
Andres *et al.* [36]	Multicenter randomized open label	76	High risk of DGF	MMF steroids	Basiliximab CsA on days 7–10	Basiliximab CsA on day 0	25% vs. 15%†‡	NS	SCr 178 μmol/l vs. 178 μmol/†‡	NS
Kovarik *et al.* [38]	Multicenter single arm	32	Normal	Azathioprine steroids	Basiliximab CsA on day 10‡		50%¶	–	SCr 188 μmol/l	–
Complete CNI avoidance										
Vincenti *et al.* [42]	Multicenter single arm	98	Low	MMF steroids	Daclizumab no CNI unless rejection occurred**		53%	–	SCr 139 μmol/l	–

Table 3. (contd)

Trial	Design	Population size (*n*)	Population risk status	Maintenance immuno-suppression	CNI minimization group	Control group	BPAR at 1 year in CNI minimization group versus controls (% patients)	*P*	Renal function at 1 year in CNI minimization group versus controls	*P*
Tran *et al.* [41]	Single-center single arm	45	Normal	MMF steroids	Daclizumab no CNI unless rejection occurred††		31%‡	–	SCr 123 μmol/l†	–
Flechner *et al.* [43]	Single-center randomized open label	61	Normal	MMF steroids	Basiliximab sirolimus	Basiliximab CsA	6.4 vs. 16.6%	NS	eGFR 81 ml/min vs. 61 ml/min	0.008

*Includes patients in whom CNI was withdrawn at month 4 (data not shown).
†Clinically suspected and biopsy-proven acute rejection.
‡At 6 months post-transplant.
§Patients were randomized open label to either everolimus 1.5 mg or 3 mg; protocols were similar in either trial other than use of basiliximab and CsA exposure targets.
¶At 3 months post-transplant.
**38% of patients received CNI > 7 days by year 1.
††49% of patients CNI-free at 6 months.

regimen, an mTOR inhibitor, MMF, and steroids but multicenter trials are awaited for confirmation (*Grade II*). In patients who are not at high immunologic risk, efficacy appears comparable using IL-2RA induction and delayed introduction of CNI (<7 days post-transplant) versus no induction with immediate introduction of CNI (*Grade I*); again, current data require further validation.

Efficacy comparison of induction agents

Polyclonal lymphocyte-depleting agents bind to a wide range of antigens on T-cell membranes [45], leading to lytic or phagocytic cell death and prolonged depletion of T-cells. Lymphocyte-depleting agents are generally used preferentially in patients at high immunological risk. In contrast, IL-2RA agents do not deplete T-cells. Of the two available IL-2RA agents, basiliximab is a chimeric antibody and daclizumab is a humanized antibody. Both agents have comparable pharmacokinetic and pharmacodynamic characteristics and are equipotent [12,46] if an adequate dose of daclizumab is used (>3–4 mg/kg in total).

Four randomized clinical trials have compared the efficacy of IL-2RA induction versus lymphocyte-depleting agents (Table 4) [47–50]. Three studies in patients at normal or low immunologic risk have shown the incidence of rejection to be comparable with either type of induction [47–49]. For renal transplant patients at high risk of rejection, results from a large randomized, multicenter study showed a significantly lower rate of biopsy-proven acute rejection with rabbit antithymocyte globulin (rATG, Thymoglobulin®) than IL-2RA induction when used in combination with cyclosporine, MMF, and steroids [50]. All patients in the study had at least one risk factor, either relating to graft quality (cold ischemia time ≥24 h, donor age ≥50 years, donor acute tubular necrosis (ATN) or high ionotropic use, or a nonheart-beating donor) or to the recipient (retransplant, panel reactive antibody >20%, six antigen mismatch, or African descent).

In summary, in kidney transplant patients at normal or low immunologic risk, the available evidence suggests that incidence of acute rejection is comparable with IL-2RA induction or lymphocyte-depleting antibodies such as rATG (*Grade I*). In high-risk kidney transplant patients, the risk of rejection appears to be lower with rATG than with IL-2RA induction (*Grade I*).

Tolerability comparison of induction agents

Interleukin-2 receptor antagonists are the only class of immunosuppressive agents not associated with adverse events related to over-immunosuppression. No cases of cytokine release syndrome or anaphylaxis were reported

Table 4. Trials of IL-2RA induction therapy versus lymphocyte-depleting agents in renal transplant recipients.

Trial	Design	*n*	Population risk status	Baseline immuno-suppression	IL-2RA induction group	Lymphocyte-depleting induction group	BPAR at 1 year with IL-2RA versus lymphocyte-depleting induction (% patients)	*P*
Sollinger *et al.* [47]	Multicenter randomized open label	135	Normal	MMF steroids	Basiliximab CsA by day 2	antithymocyte globolin (ATGAM) delayed CsA*	19% vs. 20%	NS
Lebranchu *et al.* [48]	Multicenter randomized open label	100	Normal (25% DGF)	MMF steroids	Basiliximab CsA on day 0	rATG CsA from day 4	8% vs. 8%†	NS
Mourad *et al.* [49]	Multicenter randomized open label	105	Low or normal	Delayed CsA‡ MMF steroids	Basiliximab	rATG	10% vs. 9%	NS
Brennan *et al.* [50]	Multicenter randomized open label	277	High	CsA MMF steroids	Basiliximab	rATG	25% vs. 14%§	0.013

*CsA initiated when serum creatinine <265 μmol/l or ≥50% below baseline.
†At 6 months.
‡CsA initiated when serum creatinine <200 μmol/l.
§Mean follow-up 9.8 months.

among over 800 patients receiving basiliximab or daclizumab within clinical trials [4–9], compared with a high incidence with lymphocyte-depleting agents [48]. Hematological toxicity, notably leukopenia and thrombocytopenia, is also frequent with lymphocyte-depleting agents but is seen only rarely with IL-2RA induction [11,49,50]. Randomized trials have consistently demonstrated that the use of IL-2RA induction does not increase risk of infection compared with placebo [4–9], and meta-analyses have confirmed that IL-2RA induction is not associated with increased cytomegalovirus (CMV) infection (Table 1) [11,12]. In a study that did not use routine CMV prophylaxis, CMV infection was significantly less frequent with IL-2RA than rATG induction [48]. A meta-analysis by Webster *et al.* [11] found the relative risk of CMV infection among patients taking part in seven randomized, controlled trials to be 0.82 (95% CI: 0.33–1.36, NS).

The long-term risk of malignancy following kidney transplantation is not increased by use of IL-2RA induction [11,46,51]. The meta-analysis by Webster *et al.* [11], using data from nine randomized trials, indicated that the relative risk of malignancy with IL-2RA induction versus no induction was 0.67 (95% CI: 0.33–1.36, NS) (Table 1). The analysis also reported no statistically significant differences in malignancy risk with IL-2RA induction versus polyclonal antibodies. In contrast, results from the Collaborative Transplant Study suggest that non-Hodgkin lymphomas are more common in patients receiving lymphocyte-depleting agents than in patients with no induction or IL-2RA induction [51] (Table 1). Finally, a Cox multivariate analysis of data from 38 519 renal transplant recipients showed a 29% increase in relative risk of post-transplant lymphoproliferative disease (PTLD) with polyclonal lymphocyte-depleting therapy versus no induction ($P = 0.27$) and 14% with IL-2RA induction versus no induction ($P = 0.52$) [52].

In summary, symptoms of cytokine release syndrome are common with lymphocyte-depleting agents, but are not reported with IL-2RA induction (*Grade I*). Leukopenia and thrombocytopenia are also significantly less frequent with IL-2RA induction (*Grade I*). There is evidence for reduced risk of CMV infection with IL-2RA induction versus rATG in the absence of CMV prophylaxis (*Grade II*), but as CMV prophylaxis is used widely this may not be clinically relevant. Long-term follow-up of pivotal trials and registry data show no increase in risk of malignancy or PTLD with IL-2RA induction versus placebo (*Grade II*). There are registry data which suggest that incidence of PTLD may be higher with lymphocyte-depleting agents versus no induction or compared with IL-2RA induction (*Grade II*), but this has not been proved conclusively.

Pharmacoeconomics

The economic implications of IL-2RA induction have been assessed in combination with CsA, steroids and azathioprine, and results showed that there was no significant difference in mean healthcare costs with or without IL-2RA induction therapy in the first 6 months post-transplant [53]. A more detailed analysis of healthcare costs in 376 renal transplant recipients randomized to basiliximab or placebo within a dual therapy regimen (CsA and steroids) found that mean direct costs were lower with IL-2RA induction because of a reduction in the cost of managing graft function, graft loss and dialysis (e.g. €1576 lower dialysis costs with basiliximab than placebo) and fewer follow-up hospitalizations (€1622 lower with basiliximab than placebo) [54], a finding confirmed elsewhere [55].

Total direct medical costs associated with use of an IL-2RA induction agent or rATG to month 6 post-transplant have been compared in 100 renal transplant patients randomized to basiliximab or rATG in a multicenter study conducted in France; all patients received CsA, MMF, and steroids [56]. In the basiliximab group, direct medical cost savings of €1159 per patient were recorded compared with the rATG recipients, resulting from a shorter duration of initial hospital stays and fewer infectious episodes. In a further study, IL-2RA induction was compared with ATG (type of agent was not specified) in 135 renal transplant patients taking part in a 12-month randomized trial in the USA. Treatment costs were significantly lower with basiliximab than ATG ($8872 less), primarily because of the lower purchase price of basiliximab versus ATG and other savings during initial hospitalization [57].

Conclusion

Interleukin-2 receptor antagonist induction reduces the risk of acute rejection following renal transplantation compared with placebo with a side-effect profile comparable with placebo. In this regard, IL-2RA agents are unique among current immunosuppressive agents. Several studies have demonstrated successful early steroid withdrawal or CNI minimization using IL-2RAs, and these are becoming established uses for IL-2RA induction despite lack of long-term data. rATG shows increased efficacy compared with IL-2RA induction in high-risk patients, but efficacy in patients at normal immunologic risk appears to be comparable with IL-2RA induction or rATG, and both the short- and longer-term adverse event profiles of IL-2RA agents are superior to those of rATG. The cost of rATG is greater than that of IL-2RA induction agents if a course of four or more days is planned. Consequently, use of rATG may be most suitable for patients at high immunological risk, in whom the incremental efficacy benefit outweighs the additional risk of viral infection. IL-2RA induction appears to be an appropriate choice for patients who are not at high immunological risk and who could benefit from the good tolerability profile of IL-2RA agents and the option to minimize exposure to other immunosuppressive agents.

Acknowledgement

The meeting was supported by Novartis Pharma AG, including expenses and honoraria for the faculty.

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