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Induction Therapy in Renal Transplantation

An Overview of Current Developments

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Abstract

An overview of the past 10 years of clinical renal transplantation would include progress in the development of new induction protocols (non-depleting versus depleting monoclonal and polyclonal antibodies, plasmapheresis and intravenous immunoglobulins) designed to reduce the incidence and severity of rejection and adverse effects as well as improve long-term graft and patient survival. These modalities have been introduced primarily to reduce the incidence of acute rejection episodes leading to early graft loss, decrease the need for higher toxic doses of maintenance immunosuppressive drugs, such as calcineurin inhibitors, and possibly aid in the pursuit of the goal of achieving immunological tolerance and the avoidance of all long-term immunosuppressive therapy. What has resulted during the past 20 years as the use of induction agents has become more popular is the concurrent improvement in detection and treatment of acute and chronic infectious (primarily viral), and opportunistic and quasi-malignant disease accompanying the use of these agents and, therefore, their increase in popularity. However, the overall cost of therapy and the long-term results of protocols in which these agents have been used have not resulted in a definitive benefit thus far, because of the lack of sufficient numbers of defined randomised, long-term studies and the continuing introduction of newer protocols based on even more recent advances. The specific agents used for induction therapy to date, and the rationale for their introduction and mechanisms of action are discussed in this review.

Progress in the development of immunosuppressive regimens has reduced the incidence and severity of acute rejection after renal transplantation. This has resulted in improved short-term (primarily 1 year) outcomes,[1-5] but with less marked effects in the long term,[6,7] partly as a result of the continued nephrotoxicity of high-dose calcineurin inhibitors associated with chronic allograft nephropathy[8] and immunologically mediated chronic rejection.[9,10] Regimens that can yield similar short-term results but with less marked long-term deterioration[11,12] continue to be sought, and may even eventually allow the development of immunological tolerance.[13,14]

This article reviews the major changes in the combinations of therapies used in induction therapy for renal transplantation, emphasising different protocols of nondepleting monoclonal versus depleting monoclonal and polyclonal antibodies for induction therapy in combination with a reduction or avoidance of corticosteroids and calcineurin inhibitors. The new agents with novel immunological targets, such as antibodies against CD52 (alemtuzumab) and CD20 (rituximab), are discussed in detail, while

those under development but which have yet to survive the rigour of clinical trials (such as antibodies against lymphocyte function associated antigen [LFA]-1 or intracellular adhesion molecule [ICAM]-1), are also mentioned. In the presence of low early rejection rates, immunosuppressive therapy is setting new goals such as better graft function (glomerular filtration rates), reduction in adverse effects (hypertension, hyperlipidaemia and drug toxicity) and, above all, the prevention of late graft deterioration.

1. Antilymphocyte (Depleting) Antibodies

1.1 Antithymocyte Globulins

Thymoglobulin® [1], a purified pooled product of polyclonal rabbit antibody immunoglobulins directed against human thymocytes, was initially approved for treatment of acute cellular rejection, but has been used as an induction agent as well.[15] It is said to be the most potent polyclonal product available today.[16] Brennan et al.[16] compared the efficacy and safety of this rabbit antithymocyte globulin (ATG) with those of equine ATG (Atgam®) for induction in adult renal transplant recipients. Transplant recipients (n = 72) were randomised 2 : 1 in a double-blind fashion to receive rabbit ATG (n = 48) 1.5 mg/kg intravenously or equine ATG (n = 24) 15 mg/kg intravenously, intraoperatively, then daily for at least 6 days. By 1 year after transplantation, 4% of rabbit ATG-treated patients experienced acute rejection compared with 25% of equine ATG-treated patients ($p = 0.0014$). Rejection was less severe with the rabbit than equine ATG ($p = 0.02$). No recurrent rejection occurred with rabbit ATG compared with 33% with equine ATG (not significant). Patient survival was not different, but the composite endpoint of freedom from death and graft loss or rejection, 'event-free survival', was superior with rabbit ATG (94%) compared with equine ATG (63%; $p = 0.0005$). Leukopenia was more common with rabbit than equine ATG (56% vs 4%; $p < 0.0001$) during induction. The incidence of cytomegalovirus (CMV) disease was less with rabbit than equine ATG at 6 months (10% vs 33%; $p = 0.0025$). Brief (7-day) induction with rabbit ATG resulted in less frequent and less severe rejection, an improved event-free survival, less CMV disease, fewer serious adverse events, but more frequent early leukopenia than induction with equine ATG.

Szczech et al.[17] reported a meta-analysis of early trials using ATG induction therapy and showed a benefit on graft survival at 2 years of 6% over conventional therapy and a similar benefit at 5 years for presensitised patients. Recent clinical trials report similar results comparing rabbit ATG induction accompanied with long-term tacrolimus-based triple therapy versus induction with ATG followed by tacrolimus or ciclosporin (cyclosporine) therapy (all combined with azathioprine and corticosteroids),[18] or rabbit ATG induction followed by sirolimus monotherapy.[19] In the three-arm, 6-month, open-label, randomised, prospective study by Charpentier et al.,[18] the acute rejection rate was significantly lower in the ATG-tacrolimus group (23%) compared with ATG-ciclosporin (37%) and tacrolimus triple therapy (33%) groups. Infectious and adverse haematological complications were higher in the tacrolimus triple therapy than in the ATG-induction groups.

More recently, Shapiro et al.[20] reported 92% 1-year graft survival in 150 patients receiving rabbit ATG induction followed by corticosteroid-free tacrolimus monotherapy. However, the incidence of acute rejection in this series was relatively high at 37%; only 7% required prolonged treatment with any agent other than tacrolimus.

Goggins et al.[21] reported a prospective, randomised study of three to six doses of rabbit ATG induction (1 mg/kg per dose) in 58 adult deceased-donor renal transplant recipients. The transplant recipients were randomised to receive intraoperative or postoperative ATG induction therapy. Intraoperative ATG administration was associated with significantly less delayed graft function (DGF) and lower mean serum creatinine on postoperative days 10 and 14 ($p < 0.05$). Postoperative length of stay was also significantly shorter for the intraoperative ATG patient group. The results of this study indicated that

1 The use of trade names is for identification purposes only and does not imply endorsement.

intraoperative rabbit ATG administration in adult deceased-donor renal transplant recipients is associated with a significant decrease in DGF and better early allograft function in the first month after transplant.

Recently, Agha et al.[22] reported their experience in the use of short-course induction with rabbit ATG 3 mg/kg intravenously, intraoperatively, followed by 1.5 mg/kg daily for 2 days. The study was a prospective, nonrandomised trial of 40 consecutive adult renal transplant recipients receiving rabbit ATG induction for 3 days and followed for 1 year. A historical group of 48 patients who received 7 days of rabbit ATG served as control. At 1 year, acute rejection (5% vs 4%), graft survival (95% vs 98%) and patient survival were similar; a composite endpoint of freedom from death, rejection or graft loss, the event-free graft survival, was similar as was the safety profile. Three-day induction with rabbit ATG was as effective and safely used as 7 days.

1.2 Alemtuzumab

Alemtuzumab (campath-1H), is a humanised monoclonal antibody directed against the membrane glycoprotein CD52, which is found on T cells, B cells, monocytes/macrophages, natural killer cells, CD34+ stem cells, granulocytes and red blood cells in relatively descending binding concentrations.[23-26]

1.2.1 Early Experience

The Cambridge group, headed by Calne, performed the first series of human renal transplants using alemtuzumab induction therapy as prophylaxis against rejection in combination with low-dose ciclosporin monotherapy.[27] This trial of 31 patients used two doses of alemtuzumab, 20mg each, given on the day of the transplant and shortly afterwards, after premedication with intravenous corticosteroids. No additional corticosteroids were administered. Ciclosporin monotherapy trough levels were in the range of 100–150 ng/mL. Twenty-nine patients had sustained functioning grafts 5 years later.[28] There were six separate episodes of corticosteroid-responsive rejection, with one case reported of an almost acellular vasculitic rejection also treated with corticosteroids. Acute humoral rejection was not described and the issue of true immunological tolerance was not addressed,[27] although Calne coined the term prope (near) tolerance.

1.2.2 Clinical Trials in the US

Kirk and colleagues[29] were the first to use alemtuzumab in the US. They tested whether the need for maintenance immunosuppression might be eliminated by administration of multiple doses. A series of seven nonsensitised recipients of living donor kidneys were treated perioperatively with alemtuzumab and followed postoperatively without targeted additional immunosuppression. Alemtuzumab was given intravenously at 0.3 mg/kg per dose. Six patients received three doses in the peritransplant period: four on days −5, −3 and −1, and two on days −3, −1 and +2. One received four doses on days −1, +1, +3 and +5. This represented up to a 200% increase over that previously reported for organ transplantation.[30] Profound peripheral lymphocyte (and monocyte depletion) occurred, but all patients developed reversible rejection episodes within the first month that were characterised by monocytic (not lymphocytic) infiltrates with only rare T cells in the peripheral blood or allograft. Most were reversed with corticosteroid therapy and one required muromonab CD3 (OKT3) as well. Sirolimus maintenance therapy was then initiated. There were no late rejections. In this series, T-cell depletion did not induce tolerance to the allograft.

The second clinical trial was conducted by Knechtle and colleagues[31] at the University of Wisconsin. Twenty-four living donor kidney transplant recipients in the initial study received two doses of alemtuzumab 20mg each on day 0 and day 1, and were premedicated with corticosteroids. They were then continued on maintenance sirolimus monotherapy. Although most patients demonstrated immunological quiescence, 30% experienced significant early rejection, usually between 2 and 3 weeks postoperatively. These rejections were typically humoral rather than cellular. Some required plasmapheresis and aggressive antibody therapy. Next, using a modification in this protocol, the initial dose of alemtuzumab was given the day before transplantation followed by a dose of rabbit ATG 1.5 mg/kg, on day 2. A 2-week course of corticosteroids was also added. Nevertheless, of five patients, three experienced acute rejection. The principal lesson learned

from these 29 patients was that immunosuppression using alemtuzumab, maintenance monotherapy with sirolimus was not adequate to prevent (humoral) immunity in patients with such predisposition, despite lymphocyte depletion, and that perhaps a calcineurin inhibitor might have been preferable.

Subsequently, the same group[32] reported a more extensive (single-centre) nonconcurrent retrospective study comparing patients who received two doses of alemtuzumab at the time of renal transplant in combination with a low dose of corticosteroids (methylprednisolone 10 mg/day), mycophenolate mofetil (MMF) and either tacrolimus or ciclosporin (n = 126) with those who received either a (previous) anti-interleukin (IL)-2 receptor (IL-2R) [nonlymphodepleting] humanised monoclonal antibody (n = 799) protocol, a previous ATG protocol (n = 160) or other antibody treatment (n = 156). The latter three groups also received in combination, a calcineurin inhibitor, MMF and higher-dose corticosteroids. The alemtuzumab group overall experienced less rejection than the other three groups (p = 0.037). A subgroup with DGF, if treated with alemtuzumab, experienced even less rejection and improved graft survival statistically p = 0.0096 and 0.0119, respectively, than the control groups. There was no difference in infection or malignancies among the four groups. Alemtuzumab was well tolerated in renal transplanted patients and led to significant reductions in incidence of rejection. Patients with DGF experienced significantly improved graft survival.

The group at the University of Pittsburgh[33] suggested that lymphoid depletion before rather than after transplantation would reduce the anticipated donor-specific response and so avoid high dosage and multiple immunosuppressive agents in maintenance. It was proposed that tacrolimus monotherapy could then be markedly reduced long term to between one and three doses per week, and that this would also facilitate clonal exhaustion. Lymphoid depletion was first attempted with an infusion of high-dose rabbit ATG (5 mg/kg) accompanied by pulse methylprednisolone to prevent cytokine release. Subsequently, one 30mg dose of alemtuzumab was used instead of the ATG. Three groups were retrospectively compared: the historical controls with no pretreatment (n = 152), the rabbit ATG pretreatment group (n = 101) and the alemtuzumab pretreatment group (n = 90).

Patient and graft survival were not significantly different in either of the depleted groups versus the historical controls (p = 0.12–0.59). Alemtuzumab-pretreated patients had the best early mean serum creatinine, but there were no differences at 1 year. However, there were markedly different incidences and times to acute rejection. In the ATG-pretreated patients, the onset of rejection was earlier and the incidence was higher ($p < 0.001$) than in either the alemtuzumab or historical control without antibody induction. The incidence of rejection during the first 6 months after alemtuzumab pretreatment was 1%.

Spaced weaning was attempted in 91 (90.1%) of the 101 recipients of the ATG pretreatment group. In 45% of these patients, daily maintenance therapy was resumed because of acute rejection. Spaced weaning was also attempted in 83 (92.2%) of the 90 patients of the alemtuzumab pretreatment group. With follow-ups of 12–18 months, 62 (74%) of the 83 alemtuzumab-treated patients are on daily monotherapy and only ten (12%) are receiving more than a single agent. The conclusion of this still relatively early follow-up was that after lymphoid depletion with alemtuzumab, kidney transplantation can be readily accomplished under minimal immunosuppression with less dependence on late maintenance immunosuppression.

Tan and colleagues[34] reported their experience of three living related donor renal transplantation HIV-positive recipients preconditioned with alemtuzumab 30mg followed by low-dose tacrolimus monotherapy. All three patients had good graft function and none had experienced acute rejection.

Alemtuzumab has not been as promising using other agents such as deoxypergualin[35] and sirolimus plus MMF maintenance.[36]

1.2.3 The University of Miami Experience

In an attempt to reduce both early and long-term (nephrotoxic) calcineurin inhibitor maintenance dosage and totally eliminate maintenance corticosteroids, Ciancio and colleagues[37] used alemtuzumab as induction therapy in first deceased donor and non-human leukocyte antigen (HLA) identical living donor renal transplantation. Forty-four *de novo* renal allograft recipients were treated with alem-

tuzumab 0.3 mg/kg on day 0 and day 4 postoperatively, which was preceded by methylprednisolone boluses. Maintenance target 12-hour tacrolimus trough levels of 5–7 ng/mL were operational from the outset as well as a (reduced) MMF dosage of 500mg twice daily. No corticosteroids were planned to be given after the first week. In an early report with a median follow-up of 9 (range 1–19) months, patient and graft survival were each at 100%. Biopsy-proven acute rejection was diagnosed in four patients. Four patients developed infections that required hospitalisation. Thirty-eight remained without the need for long-term corticosteroid therapy. The combination of alemtuzumab, low doses of tacrolimus and MMF, and avoidance of maintenance corticosteroid use seems to be safe and effective for kidney transplant recipients.

However, later reports and experience have suggested that a higher incidence of biopsy acute rejection may exist in the African American and Hispanic subgroups even with alemtuzumab.[38]

2. Anti-Interleukin-2 Receptor (Nondepleting) Antibodies

Daclizumab and basiliximab, humanised and chimeric IgG monoclonal antibodies, have a high specificity and affinity for the α subunit of the lymphocyte IL-2R (CD25) on the surface of activated T cells. These agents inhibit the binding of IL-2 to IL-2R, competitively inhibiting IL-2-mediated activation and proliferation of T cells, with the goal of preventing acute rejection without affecting the preexisting and nonspecific immune responses in the recipients.[39,40] Although both agents appear to have similar effectiveness and safety, daclizumab is specifically described here except for a few comparative studies between the two agents.

2.1 Daclizumab in Kidney Transplantation

Vincenti et al.[41] reported the first clinical trial using a humanised anti-IL-2R antibody in renal transplant recipients. This open-label phase I trial was to assess the safety, immunogenicity, pharmacokinetics and pharmacodynamics of daclizumab. Daclizumab was found to be free of adverse effects.[41] Only 1 of 12 patients who received renal transplants had a rejection episode and it was treated successfully with muromonab CD3.

These results prompted two phase III randomised placebo-controlled clinical trials of daclizumab to prevent acute rejection.[42,43]

A total of 535 recipients of first deceased donor renal transplants were randomised to have their first dose of daclizumab or placebo administered as a 15-minute intravenous infusion immediately before transplantation and once every 2 weeks thereafter for a total of five doses. In one of these studies, 126 daclizumab recipients and 134 patients receiving placebo were also given ciclosporin-based triple immunosuppressive therapy.[42] The second study, of 275 patients, was otherwise identical (daclizumab 116 patients, placebo 111 patients) but concurrent immunosuppression consisted of only ciclosporin and corticosteroids (dual therapy).[43] The primary efficacy endpoint of both studies was the incidence of biopsy-proven acute rejection at 6 months after transplantation. In both studies, the addition of daclizumab significantly reduced the rate of acute graft rejection when compared with placebo.[42,43] At 6 months, the acute rejection rate in patients treated with daclizumab was 22% versus 35% with placebo ($p = 0.03$),[42] and 28% versus 47% ($p = 0.001$).[43] The graft survival rates after 1 year were higher in daclizumab recipients in both studies, i.e. 95% and 88% for the daclizumab groups, and 90% and 83% for the placebo groups. Daclizumab was also associated with significant reduction in the mean number of rejection episodes per patient. Daclizumab was not associated with cytokine-release syndrome or formation of anti-idiotype antibodies, increased fungal or CMV infections, or malignancies.[42,43]

Results from a pooled analysis of 1-year efficacy data from the two phase III studies showed the biopsy-proven acute rejection rate at 1 year to be significantly reduced overall by 36%.[44]

Bumgardner et al.[45] then reported the 3-year outcome of the two pooled phase III randomised, placebo-controlled, multicentre clinical trials. The graft survival was not significantly different between placebo- and daclizumab-treated patients in the triple-therapy group (83% vs 84%) or in the double-therapy (78% vs 82%). Pooled patient survival was no different either (placebo 91% and daclizumab 93%). The decreased incidence of acute

rejection at 6 months post-transplant in daclizumab-treated patients was not accompanied by improved graft survival at 3 years. A longer-term follow-up period or more patients may have been needed for any improvement or any detrimental factors in daclizumab usage to be clarified.[45]

2.1.1 Daclizumab in Combination with Tacrolimus, Mycophenolate Mofetil (MMF) and Corticosteroids

Ciancio et al.[5] tested the addition of daclizumab to a tacrolimus plus MMF-based immunosuppressive protocol to evaluate whether there might be an additional reduction of the risk of rejection in a nonrandomised, prospective study of 233 sequential recipients of first renal transplantations. These were retrospectively compared with a control group of 225 renal transplant recipients who received a 10-day course of muromonab CD3 induction with otherwise similar tacrolimus, MMF and methylprednisolone maintenance. The daclizumab dose was 1 mg/kg on the day of surgery and every other week thereafter for a total of five doses. Follow-up was for 1 year for the incidence of biopsy-proven acute rejection, patient and graft survival and adverse events.

One-year patient and graft survival for the daclizumab group was, respectively, 98% and 96% versus 96% and 94% for the muromonab CD3 group (not statistically different). Acute rejection rates (≈6 months) were lower in the daclizumab group than the muromonab CD3 group: 5 (2.1%) versus 16 (7.1%) [p = 0.011]. The incidence of infection requiring hospitalisation was lower with daclizumab (7.3% vs 16%; p < 0.0036) with perhaps a similar trend with CMV infections (1.6 % vs 4%; p = 0.14). In an updated report of additional recipients (n = 305) the efficacy and safety of daclizumab was still observed. Seven (2.3%) of the rejection episodes occurred during the first 6 months postoperatively.[38]

Several other trials have demonstrated the efficacy of daclizumab with MMF, corticosteroids and a calcineurin inhibitor (tacrolimus or ciclosporin) in preventing acute rejection.[46-49] In a short report from a double-blind placebo-controlled trial among 75 patients, there was a 6-month acute rejection rate of 12% in daclizumab-treated patients compared with 20% in those receiving placebo. All received first renal transplants from either living or deceased donors and concurrent prednisone, MMF and ciclosporin as baseline immunosuppression.[47]

In another nonrandomised trial evaluating the combination of daclizumab with MMF plus tacrolimus or ciclosporin in 58 patients who received living donor renal allografts, the 3-month acute rejection rate was 7% in daclizumab-treated recipients compared with 15% in a group of 27 matched non-treated controls. Patient and graft survival was not statistically significantly different between groups.[48]

2.1.2 Limited Doses of Daclizumab in Primary Kidney Transplantation

Despite the recommended five-dose regimen for daclizumab, recent data suggest that one- and two-dose regimens provide effective blockade of IL-2R for up to 10 weeks.[50]

Data from a multicentre trial of 40 adult recipients indicate that a two-dose regimen of daclizumab 1 mg/kg given intravenously on days 0 and 10 after transplantation in combination with tacrolimus and MMF results in blockade of the IL-2Rα chain for >10 weeks.[50] The same findings were reported from a smaller trial of 12 patients that compared one- and two-dose regimens.[50] In this trial, the difference in receptor saturation levels (saturation of IL-2Rα on circulating peripheral blood lymphocytes) between one preoperative dose of 2 mg/kg versus one preoperative dose of 2 mg/kg followed by 1 mg/kg on day 14 was 42 versus 70 days. This reached statistical significance (p = 0.01).[51] Patients were also treated with tacrolimus (n = 11) or ciclosporin (n = 1), MMF and corticosteroids. There were no rejection episodes in 6 months of follow-up.

Ahsan et al.[52] reported a prospective study comparing a single intraoperative dose of daclizumab (2 mg/kg) versus noninduction in 100 first deceased donor recipients treated with maintenance tacrolimus, MMF and prednisone (daclizumab 50 patients, no induction or control 50 patients). During the first 6 months, there were three (6%) episodes of first biopsy-confirmed acute rejection in the limited daclizumab group and eight (16%) in the control group (p < 0.05). Twelve-month patient and graft survival were not statistically different (100% and 80% vs 100% and 96%). There were no adverse reactions reported in the group receiving daclizumab. These studies[50-52] appeared to demonstrate that

a limited dose of daclizumab when combined with a calcineurin inhibitor, MMF and corticosteroids allowed significant reduction in early renal allograft rejection without adverse effects, and without the need for a more prolonged course of daclizumab as originally recommended.

2.1.3 Daclizumab Induction Therapy in High-Risk Patients

It has been reported that African American kidney recipients have an increased incidence of acute rejection, DGF and lower graft survival; results from various trials indicate that daclizumab may also be effective in this ethnic group.[53-56]

Tacrolimus and MMF have each been demonstrated to be effective in lowering the incidence of acute rejection when combined with other agents in kidney transplantation.[57,58] Limited data are available on these agents in conjunction with daclizumab, particularly in higher-risk patients. Ciancio et al.[56] compared racial differences in the incidence of acute rejection between African American, Hispanic and Caucasian first renal transplant recipients using daclizumab, tacrolimus, MMF and corticosteroid-based immunosuppression.

Of the 233 patients receiving daclizumab as induction therapy, 37 (16%) were African American, 85 (36.5%) were Hispanic and 111 (47.5%) were Caucasian. All patients received maintenance tacrolimus, methylprednisolone, MMF and daclizumab 1 mg/kg administered on the day of surgery, and every other week for a total of five doses. There were no significant demographic differences between the three groups, i.e. regarding age, original disease, panel reactive antibodies, histocompatibility match, donor age, or average cold and warm ischaemia time. At 1 year, the results are as follows: biopsy-proven acute rejection 8.1% in the African American, 4.7% in the Hispanic and 4.55% in the Caucasian group, and the serum creatinine levels of the three groups did not differ (1.5 ± 1 mg/dL for the African American group, 1.3 ± 0.4 mg/dL for the Hispanic and 1.3 ± 0.7 mg/dL for the Caucasian; $p = 0.172$). There were no significant differences in overall patient or graft survival between the three groups at 12 months: 97% and 95% in the African American, 98% and 98% in the Hispanic and 96% and 95% in the Caucasian group ($p = 0.856$ and 0.536, respectively). This trial demonstrated the antirejection efficacy of combining daclizumab, tacrolimus and MMF in a reasonably large immunologically high-risk group.[56]

In another nonrandomised prospective study, 49 renal transplant recipients (29 African American and 20 Hispanic) were treated with daclizumab 1 mg/kg for five doses, with ciclosporin, MMF and prednisone. They were compared with a simultaneous cohort of 56 (31 African American and 25 Hispanic) renal transplant recipients receiving the same immunosuppression without daclizumab induction therapy. Acute rejection rates were lower in the daclizumab group than in the control group: 26.4% versus 49.3% per patient-year. Eight recurrent rejections in six patients occurred in the control group and none in the daclizumab group.[54]

2.1.4 Daclizumab and Calcineurin Inhibitor-Sparing Regimen in Renal Transplantation

Another potential use of daclizumab is to eliminate or spare the use of calcineurin inhibitors from immunosuppressive regimens.[59] Two noncomparative studies have reported the effect of completely eliminating calcineurin inhibitors from the immunosuppressive protocol.[60,61] Both used similar immunosuppressive regimens. The initial dose of daclizumab was 2 mg/kg, and then 1 mg/kg for four more doses, and maintenance was with MMF and corticosteroids only.

One calcineurin inhibitor avoidance trial enrolled 98 recipients of primary deceased or living donor kidneys at low immunological risk.[60] Biopsy-proven rejection was diagnosed in 48% of patients during the first 6 months and in 53% by 12 months after transplantation. The median time to the first biopsy-proven rejection among patients who experienced this event during the first 6 months was 39 days. At 1 year post-transplant, 62% of patients had received calcineurin inhibitors for >7 days, predominantly because of rejection. The other study consisted of 45 consecutive recipients of renal allograft. Incidence of biopsy-proven rejection was 31% and this occurred early (median 10 days). However, 49% of patients were spared ciclosporin maintenance therapy.[61] Both studies reported good renal function in patients spared calcineurin inhibitors. These calcineurin inhibitor avoidance studies, partially successful in preventing acute rejection, provided benefits to a sizable minority of patients who

have not required long-term calcineurin inhibitor therapy;[60,61] however, the long-term results remain to be evaluated.

2.1.5 Daclizumab and Corticosteroid-Sparing Regimens

The use of corticosteroids is associated with hypertension, diabetes mellitus, hyperlipidaemia, osteopenia, weight gain and cushingoid appearance. As a result, in recent years, a corticosteroid-free immunosuppressive protocol using daclizumab has become popular to decrease or eliminate these adverse effects, to improve the post-transplantation metabolic state, and to promote patient and graft survival.[62,63]

Cole et al.[63] attempted corticosteroid-free renal transplantation in 57 patients treated with daclizumab, MMF and ciclosporin. At 1 year, patient and graft survival were 95% and 89%, respectively. Fourteen patients (25%) experienced rejection, which was readily reversed with corticosteroids in 13; one patient required muromonab CD3. Five patients required hospitalisation for infection and no patients developed lymphoproliferative disease. At baseline, 17 patients required three or more antihypertensive medications, compared with only two patients at 1 year. Three of 43 nondiabetic patients developed diabetes during the study, a lower than anticipated incidence because of concurrent calcineurin inhibitor therapy. There was no significant reduction in lumbar or femoral bone density. In conclusion, corticosteroid withdrawal is feasible in the majority of kidney transplant recipients, albeit with a certain risk for acute rejection episodes, and merits further study.

Daclizumab in Combination with Tacrolimus, MMF and Corticosteroid-Free Immunosuppression

Rostaing et al.[64] reported a 6-month, open-label, multicentre, parallel-group study involving 538 renal transplant patients randomised to daclizumab, tacrolimus and MMF (n = 260) or a tacrolimus, MMF plus corticosteroid regimen (n = 278) as a control group. Of the patients who completed the study, 88.8% in the daclizumab group were free from corticosteroid therapy at month 6 (they received a single dose of 500mg methlprednisolone on the day of surgery [day 0]). The incidence of biopsy-proven acute rejection was 16.5% in both treatment groups. Compared with the tacrolimus, MMF plus corticosteroid regimen, a significantly reduced incidence of new-onset type 2 diabetes (5.4% vs 0.4%; $p = 0.003$) was found with corticosteroid-free immunosuppression. Corticosteroid-free immunosuppression with daclizumab, tacrolimus plus MMF regimen is as effective at preventing acute rejection after renal transplantation as a standard triple regimen of tacrolimus, MMF and corticosteroids.

2.1.6 Daclizumab Induction Therapy in Patients with Delayed Graft Function

DGF is defined as the need for haemodialysis within the first week after transplantation. It predisposes to acute rejection episodes and has been shown to be a predictor of decreased short- and long-term graft survival. In a study reported by Hong and Kahan,[65] six consecutive patients deemed to be at high risk for DGF were treated with sirolimus (2–12 mg/day), plus daclizumab or basiliximab, and corticosteroids, withholding inception of ciclosporin therapy until the serum creatinine levels fell below 3.0 mg/dL. During the first 2 months post-transplant, none of the patients displayed clinical or histopathological evidence of acute rejection episodes. All patients recovered renal graft function within 8 weeks post-transplant.

A small retrospective review of 14 consecutive kidney transplant recipients, used a loading dose of daclizumab 2 mg/kg followed by a second dose in some patients, plus maintenance therapy with MMF and sirolimus to allow delayed administration of a calcineurin inhibitor in renal transplant patients who developed DGF.[66] Nine patients required dialysis after transplantation and two (14%) experienced acute rejection within the first month. No grafts were lost during the period of follow-up (1–6 months).[66]

Cantarovich et al.[67] reported the use of basiliximab (7 patients) and daclizumab (4 patients) in 11 adult recipients with acute renal dysfunction. Calcineurin inhibitor therapy was reduced or withheld over 21 ± 51 days with no acute rejection episodes and this strategy allowed serum creatinine levels to return to baseline.

In conclusion, the use of daclizumab in patients with DGF or acute renal dysfunction may allow the delayed introduction or avoidance of calcineurin inhibitor therapy without significantly increasing

the risk of acute rejection or affecting graft or patient survival, but long-term follow-up is needed.

2.1.7 Daclizumab as Induction Therapy for Retransplantation

The primary goal of a study in patients undergoing retransplantation was to assess the efficacy of daclizumab induction in patients with previous transplants receiving tacrolimus and MMF-based immunosuppression.[68] Four had previous liver transplants (group A), 16 had a previous renal transplant (group B) and three had a previous simultaneous pancreas-kidney transplant (group C). All underwent renal transplantation except one patient in group B who underwent a pancreas transplant. All received daclizumab (1 mg/kg) on the day of surgery and every other week for a total of five doses. MMF was started on day 1 (1 mg twice daily) and adjusted for adverse effects and white blood cell count. Tacrolimus was withheld until the serum creatinine level was <4 mg/dL and intravenous corticosteroids were initially given three times daily, with a subsequent weaning schedule. At 1 year, acute rejection rates were 0% in group A, 12.5% in group B and 0% in group C. Mean serum creatinine was 1.3 ± 0.28 mg/dL (range 1.1–1.5) for group A, 1.45 ± 0.68 mg/dL (range 0.8–2.9) for group B and 0.96 ± 0.058 mg/dL (range 0.9–1) for group C. The patient with the pancreas transplant had normal fasting blood sugar off insulin. Few complications have occurred and no CMV infection was found. Overall 1-year actuarial patient and graft survival are both 100%. In summary, daclizumab, tacrolimus and MMF appear to be safely used and potent immunosuppressive agents when used together, which may reduce acute rejection episodes in patients with previous transplants. Daclizumab as induction therapy is an addition to the armamentarium of immunosuppressive regimens, especially in patients undergoing retransplantation.[68]

2.2 Basiliximab

The clinical efficacy of induction therapy with intravenous basiliximab (two infusions only within the first 4 days postoperatively) in the prevention of acute renal graft rejection has been assessed in four well designed, randomised, double-bind, multicentre, placebo-controlled trials, and each has shown similar results to those with daclizumab.[69-72]

Two meta-analyses confirmed that basiliximab was more effective than placebo in the reduction of acute rejection at 6 months after renal transplantation (acute rejection occurred in 25.9% vs 38.1%[73] and 28.8% vs 44.4%;[74] $p < 0.0001$ for both meta-analyses). Keown et al.[74] reported that basiliximab also reduced the incidence of biopsy-proven acute rejection (25.1% vs 36.8%) and corticosteroid-resistant rejection episodes requiring antibody therapy (10.7% vs 48.7%) compared with placebo ($p < 0.0001$). In conclusion, basiliximab reduces acute rejection in renal transplant recipients when combined with standard dual or triple immunotherapy.[70-76]

3. Recent Comparisons of Novel Immunological Agents

3.1 Comparison of Daclizumab and Basiliximab as Induction Therapy

Preliminary data suggest basiliximab[37,69-75] and daclizumab[5,42-45,75,76] have similar efficacy in the prevention of acute rejection in renal transplant recipients. Nair et al.[77] reported a small, open-label, prospective study among 23 renal transplant recipients comparing the efficacy of daclizumab (1 mg/kg for five doses) versus basiliximab (20mg on day 0 and day 4 after transplantation). Baseline immunosuppression consisted of ciclosporin, MMF and prednisolone. There was no significant difference in the rate of acute rejection (10% with basiliximab and 7.7% with daclizumab) and time to first rejection episode was 8 days with basiliximab versus 6 weeks with daclizumab. There was no difference in patient and graft survival (100%) between the two groups at 10 months follow-up.

A recent study assessed the efficacy and tolerability of bolus rabbit ATG (Fresenius®) [9 mg/kg] for induction treatment in renal transplant recipients by comparing the results with those from equal numbers of matched controls who received induction with either conventional doses of ATG (3–5 mg/kg for 7–14 days) or anti-IL-2R antibodies (daclizumab 1 mg/kg or basiliximab 20mg on days 0 and 4). Acute rejection episodes were low in all

three groups (ATG bolus [21.7%], conventional ATG [26.0%] and the anti-IL-2R antibody [21.7%]), with similar patient and graft survival between the three groups.[78]

Acute rejection is a risk factor for development of chronic rejection and both daclizumab and basiliximab have been shown to reduce the incidence of acute rejection without increasing the incidence of opportunistic infections or malignancy. Further studies are needed to evaluate the overall effect of these agents on the long-term survival of patients and allografts.[75]

3.2 Alemtuzumab versus Basiliximab: Prednisone-Free Maintenance Immunotherapy

Kaufman and colleagues[79] recently reported a nonrandomised, retrospective, sequential study comparing outcomes in kidney transplant recipients induced either with alemtuzumab (n = 123) or basiliximab (n = 155) in combination with a prednisone-free maintenance protocol using tacrolimus and MMF.

The 1-year actual patient survival rates for recipients of alemtuzumab and basiliximab were 96.8% and 99.4%, respectively. The 1-year actual death censored graft survival rates for recipients of alemtuzumab and basiliximab were 99.2% and 99.4%, respectively. There was no significant difference for either finding. A lower rate of early (<3 months) rejection was observed in the alemtuzumab versus the basiliximab group (4.1% vs 11.6%), but the rates for both groups were equivalent at 1 year (14.9% and 13.5%; not significant). At 1 year, there was no significant difference in serum creatinine levels, at 1.42 ± 0.59 mg/mL for the alemtuzumab group and 1.36 ± 0.48 mg/mL for the basiliximab group. CMV infection occurred in 4% and 5% of recipients in the two groups, respectively. The incidences of CMV in patients not previously exposed to CMV who received organs from donors with positive CMV serology in the alemtuzumab and basiliximab groups were 21% and 19%, respectively. In summary, alemtuzumab induction therapy was similar in efficacy to basiliximab in a prednisone-free maintenance immunosuppressive protocol for an ethnically diverse population of kidney transplant recipients.

3.3 Antithymoctye Globulin (ATG) versus Basiliximab

Brennan and colleagues[80] reported a prospective, randomised, international study comparing a short course of rabbit ATG (1.5 mg/kg intraoperatively, before graft reperfusion and then for 4 more days; n = 141) and basiliximab (20mg intravenously before graft reperfusion, followed by a second infusion on day 4; n = 137) in patients at high risk for acute rejection or DGF who received a renal transplant from a deceased donor. Compared with the basiliximab group, the ATG group had lower incidences of acute rejection (15.6% vs 25.5%; p = 0.02) and acute rejection that required treatment with antibody (1.4% vs 8.0%; p = 0.005). There was a similar incidence of DGF (40.4% and 44.5% for the ATG and basiliximab groups, respectively). The incidences of all adverse events, serious adverse events and cancers were also similar between the two groups. Patients receiving ATG had a greater incidence of infection (85.8% vs 75.2%; p = 0.03) but a lower incidence of CMV disease (7.8% vs 17.5%; p = 0.02).

Among patients at high risk for acute rejection or DGF who received a renal transplant from a deceased donor, induction therapy consisting of a 5-day course of ATG, compared with basiliximab, reduced the incidence and severity of acute rejection but not the incidence of DGF.

3.4 Alemtuzumab versus ATG versus Daclizumab

Ciancio and colleagues[81] reported the only randomised trial using three different antibody induction agents in 90 deceased-donor first renal transplant recipients. Group A received murine ATG, group B alemtuzumab and group C daclizumab. Maintenance immunosuppression included tacrolimus and MMF in all three arms, and methylprednisolone in groups A and C only. The targeted trough tacrolimus level was 8 and 10 ng/mL for groups A and C, respectively, with a targeted MMF dosage of 1g twice daily. In group B, target trough tacrolimus level was 4–7 ng/mL (to reduce long-term nephrotoxicity), with 500mg 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. Acute rejection rates at 1 year were equivalent, i.e. 5 of 30 in all three groups (≈16.6%). In group B, there was slightly lower renal function at 1 month but no difference at 1 year. There was also significantly more leukopenia, but a greater percentage of T regulatory cells and number of Fox-P3 messenger RNA copies, respectively, by flow cytometry and semiquantitative polymerase chain reaction analysis in group B.

This preliminary analysis has indicated that in the alemtuzumab induction group, 80% of patients remained corticosteroid free at 1 year postoperatively, with lower trough tacrolimus levels and MMF doses. There were no differences in other adverse events. However, longer follow-up may not be as promising.[82]

4. Other Agents

4.1 Antibodies to Adhesion Molecules

T-cell activation by T-cell receptor engagement requires co-stimulatory molecules as well as adhesion molecules such as ICAM-1. In a randomised double-blind trial of induction therapy with the anti-ICAM-1 monoclonal antibody enlimomab compared with placebo in addition to a ciclosporin, azathioprine plus prednisone regimen in 262 deceased donor kidney recipients, enlimomab was not superior to placebo in preventing acute rejection episodes or DGF in a randomised double-blind study.[83]

LFA-1 is an adhesion molecule implicated in leukocyte adhesion to the endothelium, transendothelial migration and cooperation between immunocompetent cells, and cytotoxicity. In a multicentre, randomised, open-label trial, a monoclonal antibody directed against the α chain of LFA-1 (odulimomab) was compared with rabbit ATG in 101 first renal transplant patients. The rate and severity of rejection episodes as well as the incidence of infection were similar in both groups at 3 and 12 months.[82] However, 11% of the odulimomab recipients experienced rejection during the first 10 days of the treatment course compared with none of those treated with rabbit ATG. Another potential beneficial effect of these drugs is their role in diminishing the ischaemia-reperfusion injury associated with DGF. Animal studies have demonstrated a synergistic effect of the association between an anti-ICAM-1 and an anti-LFA-1 in protection against DGF;[84,85] further studies are needed to determine their role in induction therapy in kidney transplantation.

4.2 Anti-CD20 Monoclonal Antibodies

CD20 is a hydrophobic transmembrane protein that is located on pre-B and mature B cells,[86] but not plasma cells. Rituximab, a humanised chimeric monoclonal antibody that reacts with the CD20 antigen, is approved for treatment of non-Hodgkin's B-cell lymphomas and inhibits B-cell proliferation, suppressing preformed alloantibodies prior to transplantation.[87]

Supporting its use in transplantation, a high density of CD20+ lymphocytes has been found in renal transplant patients developing corticosteroid-resistant rejection.[88] A single dose of rituximab, with plasmapheresis and rabbit ATG, was convincingly effective in the treatment of 27 patients with biopsy-proven corticosteroid-resistant acute rejection.[88]

The use of rituximab, in combination with plasmapheresis and CMV hyperimmune globulin, was found to be effective in six patients with ABO-incompatible renal transplantation, avoiding splenectomy.[89] Finally, rituximab has also been successfully used to treat post-transplant lymphoproliferative disorder in patients after solid organ transplantation[90] and could help to reduce the anti-HLA antibody titre in hyperimmunised patients waiting for renal transplantation.[91]

5. Conclusion

The field of transplantation has benefited enormously from the new agents that have become available over the past decade. Among these, a number of depleting and nondepleting monoclonal and polyclonal antibodies have been introduced into clinical practice, and the use of antibody induction therapy has substantially increased over the past decade. These new induction immunosuppressive therapies and protocols have improved outcomes for renal transplant recipients by decreasing the risk of rejec-

tion and increasing the function and perhaps the 'lifespan' of the allograft.

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