

Alemtuzumab as Induction Therapy in Renal Transplantation

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Abstract

Alemtuzumab is a monoclonal antibody which causes profound lymphocyte depletion. It has gained increasing popularity as an induction agent in solid organ transplantation. The purpose of this article is to examine its mechanisms of action and to evaluate available data supporting its efficacy in this context. We therefore reviewed all published studies in which alemtuzumab was used at induction, the majority of which are non-randomized. Based on our review of the literature, we conclude that alemtuzumab is a useful induction agent, but should be used in combination with a calcineurin inhibitor to prevent early rejection. Alemtuzumab allows the use of a steroid-free maintenance regimen, and in this context, the incidence of acute rejection is at least comparable to that seen with anti-CD25 induction followed by triple therapy. Rejection episodes tend to occur much later in patients treated with alemtuzumab, necessitating ongoing vigilance in follow-up. The incidence of cytomegalovirus infection and post-transplant lymphoproliferative disorder does not seem excessive in patients treated with alemtuzumab; however, these patients may develop autoimmunity. (Trends in Transplant. 2008;2:12-23)

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Key words

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Introduction

Alemtuzumab (Campath-1H) is a humanized rat monoclonal antibody directed against the CD52 antigen, the administration of which causes profound B and T lymphocyte depletion. Alemtuzumab is now widely used in solid organ transplantation, principally as an induction agent, but also in the treatment of acute rejection. The aim of this review is to examine its mechanism of action, to evaluate the evidence available supporting its efficacy as an induction agent in renal transplantation, and to identify potential adverse events associated with its use in this context, including infection, autoimmune disease, and post-transplant lymphoproliferative disorders (PTLD).

Alemtuzumab – mechanism of action

CD52, the antigen to which alemtuzumab binds, is found on the surface of B and T lymphocytes, monocytes, macrophages, dendritic cells (DC), and natural killer (NK) cells, as well as on cells lining the male reproductive system. CD52 is a small glycoprotein comprising a 12 amino acid core attached to the cell membrane by a glycosyl phosphatidylinositol anchor¹. Although it has no intracellular domain, cross-linking can provide a co-stimulatory signal to T-cells². CD52 is abundantly expressed on the surface of lymphocytes, and administration of alemtuzumab leads to lymphocyte lysis via complement activation and antibody dependent cellular cytotoxicity. Alemtuzumab-induced lymphocyte depletion is rapid (occurring within 24-48 hours of administration) and long-lasting; B-cells return within 2-12 months, but the number of circulating T lymphocytes (particularly CD4+ T-cells) may remain depressed for many years after treatment. Evidence suggests that some T-cell subsets are resistant to

alemtuzumab-induced depletion, particularly CD4+CD45RA-effector memory cells³. Proliferation of this residual T-cell population is readily suppressed by calcineurin inhibitors, leading to the assertion that alemtuzumab should be used in combination with cyclosporin or tacrolimus³. Some investigators have proposed that the use of alemtuzumab at induction may be pro-tolerogenic⁴. This concept is supported by recent studies showing that *in vitro*, alemtuzumab appears to promote the development of regulatory T-cells, as evidenced by the expression of the forkhead transcription factor FoxP3^{5,6}. It is now widely accepted that this regulatory subset, identified as CD4+CD25+FoxP3+CTLA4+ cells, can prevent autoimmune disease⁷ and may facilitate transplant tolerance⁸. Regulatory T-cells generated *ex vivo* using a CD52 antibody can effectively suppress polyclonal CD4+ and CD8+ T-cell activation and specific allogeneic CD4+ T-cell responses upon activation with primed DC *in vitro*⁵. Furthermore, in patients treated with alemtuzumab, an increase in the proportion of CD4+CD25+FoxP3+CTLA4+ lymphocytes in peripheral blood has been observed six months following treatment, suggesting that alemtuzumab may promote the generation of regulatory T-cells *in vivo* as well as *in vitro*⁶. Alemtuzumab also alters the peripheral DC repertoire; alemtuzumab induction therapy in renal transplant recipients was associated with a sustained reduction in the total number of DC and a significant shift from myeloid to plasmacytoid DC subsets⁹. Given the importance of DC as antigen presenting cells, this may be another mechanism by which alemtuzumab limits the immune response to an allograft.

Alemtuzumab – therapeutic uses

Alemtuzumab was developed in Cambridge (UK) in the early 1990s, and has been

Table 1. Pilot studies of alemtuzumab as induction therapy

Study	Immunosuppression	Follow-up time (months)	(n)	Acute rejection at 1 year (%)	Infection (%)	CMV (%)	PTLD (%)	Auto-immunity
Calne, et al. ⁴	Low-dose cyclosporin monotherapy	12	13	15.4	8.3	0	0	No
Knechtle, et al. ²⁰ Barth, et al. ²¹	Sirolimus monotherapy	36	29	44.8	96	0	0	No
Flechner, et al. ²²	Sirolimus + MMF	16	22	36.3 (16 Mo)	72.3	9	0	No
Ciancio, et al. ²³	Low-dose tacrolimus + MMF	9	44	9	9	0	0	No
Kirk, et al. ¹⁹	None	30	7	100	ND	ND	ND	Yes ³⁰
Kirk, et al. ²⁵	Deoxyspergualin induction	18	5	100	0	0	0	No
Sollinger, et al. ²⁸	Rituximab induction + MMF/prednisolone maintenance	9.5	30	43.3	56	23	0	No

CMV: cytomegalovirus; PTLD: post-transplant lymphoproliferative disease; MMF: mycophenolate mofetil; ND: not documented.

used in the treatment of hematologic malignancies (particularly chronic lymphocytic leukemia)¹⁰, in bone marrow transplantation for graft versus host disease, in autoimmune diseases (including multiple sclerosis¹¹, rheumatoid arthritis¹², and vasculitis¹³), and in solid organ transplantation. Intravenous infusion is associated with a marked “cytokine-release syndrome”, characterized by fever, rash, hypotension, and bronchoconstriction. These side effects can be limited by the concurrent administration of high-dose methyl prednisolone. Alemtuzumab is fully humanized; hence it appears to be poorly immunogenic when given as a single or small number of doses. In this context, patients are unlikely to develop anti-globulin responses which limit the use of non-humanized antibodies. However, if recurrent doses are given (particularly via the subcutaneous route), significant anti-globulin titres may develop,

as observed in patients with rheumatoid arthritis^{12,14}.

In renal transplantation, alemtuzumab was first used in the treatment of acute rejection¹⁵. Although effective in reversing rejection, there was a high incidence of serious infection; hence it has been used with caution, but continues to offer efficacy in patients with steroid-resistant acute rejection^{16,17}. Alemtuzumab is gaining increasing popularity as an induction agent since it allows the use of steroid-free maintenance regimens. It was first used for this purpose by Calne, et al. in Cambridge a decade ago⁴. In spite of the early promise shown, no large randomized trial has ever been undertaken, and most of the data available on the efficacy of alemtuzumab as an induction agent is non-randomized and retrospective. We will begin our discussions with a review of pilot studies, move on to non-

randomized studies, and finally examine the little randomized data there is available on the use of alemtuzumab in this context.

Alemtuzumab at induction – pilot studies

A number of pilot studies have been performed in an attempt to identify the best combination of immunosuppressants to use together with alemtuzumab (Table 1). All studies use intravenous methylprednisolone prior to alemtuzumab infusion in order to limit the cytokine-release syndrome associated with administration.

Alemtuzumab plus low-dose cyclosporin

The first pilot study examining the use of alemtuzumab as induction therapy was performed in Cambridge in 1997. Thirteen patients were treated with two 20 mg doses of alemtuzumab on days 0 and 1, and maintained on low-dose cyclosporin monotherapy, aiming for trough levels of 75-125 ng/ml. Two episodes of acute rejection were reported during the first year of follow-up⁴ and there was no excess of infectious complications. This prompted its use in a further 20 patients within the same centre, the five-year results of which are discussed below¹⁸.

Alemtuzumab alone

In the initial Cambridge study, Calne had raised the possibility that the use of alemtuzumab at induction may induce so-called “*prope* tolerance” (almost tolerance). With this in mind, Kirk, et al. treated seven recipients of living donor transplant kidneys with three or four doses of alemtuzumab at induction, without the use of any maintenance

immunosuppression¹⁹. All seven patients developed acute rejection within the first month post-transplantation. These rejection episodes were characterized by a monocytic rather than lymphocytic infiltration, were easily reversible, and necessitated the introduction of maintenance immunosuppression (mostly sirolimus monotherapy). This study demonstrated that in spite of the profound lymphocyte depletion observed, alemtuzumab was insufficient to prevent early rejection if used alone.

Alemtuzumab plus sirolimus

In 2003 the results of a pilot study using alemtuzumab (20 mg on days 0 and 1) as induction therapy and sirolimus monotherapy (target level: 8-12 ng/ml) were published²⁰. Surprisingly, there was a high incidence of early humoral rejection, prompting the use of thymoglobulin and a tapering dose of steroids in the final few patients recruited. In all, 13 of 29 patients had an episode of acute rejection, of which six were humoral. Nevertheless, at three years, graft and patient survival rates were good at 96 and 100%, respectively²¹. At this stage, nearly two thirds of patients were on a single maintenance immunosuppressive agent. No cases of PTLD were observed, and although 28 infectious episodes were noted, 10 of these were urinary tract infections.

There is one other pilot study in which alemtuzumab induction was combined with sirolimus along with mycophenolate mofetil (MMF) as maintenance therapy²². Twenty-two renal transplant recipients were given alemtuzumab 30 mg on days 0 and 1, followed by MMF 500 mg twice daily and sirolimus (target level: 8-12 ng/ml). At 16 months, patient and graft survival were 96 and 87%, respectively. Acute rejection occurred in 36.3%, and two of these were humoral.

These studies are of interest because they suggest that the combination of alemtuzumab and sirolimus does not prevent humoral rejection. As mentioned previously, experimental data shows that CD4+CD45RA-effector memory T-cells are resistant to alemtuzumab-induced depletion but sensitive to suppression by calcineurin inhibitors³. Taken together, these observations suggest that alemtuzumab at induction should be used in combination with cyclosporin or tacrolimus.

Alemtuzumab plus tacrolimus and MMF

This pilot study performed in Miami (USA) has provided data upon which a randomized trial was based and is therefore of importance. Forty-four patients received two doses of alemtuzumab on days 0 and 4, followed by low-dose tacrolimus monotherapy (target trough concentration: 5-7 ng/ml) and MMF (500 mg twice daily)²³. At a median of nine months follow-up, there was a 9% rate of acute rejection and 100% graft and patient survival, without an excess of adverse events. This study has been followed by a randomized trial, the preliminary results of which appear encouraging²⁴ (see later discussion).

Alemtuzumab plus deoxyspergualin

Following on from the observation that when used as a lone induction agent, acute rejection episodes following alemtuzumab showed predominant mononuclear infiltrates¹⁹ (see above), Kirk, et al. combined alemtuzumab with deoxyspergualin (DSG) at induction, without the use of maintenance immunosuppression, in a further attempt to induce tolerance²⁵. Deoxyspergualin is a synthetic derivative of spergualin, originally

isolated from the bacteria *bacillus laterosporus*. It has a wide range of immunosuppressive activities, inhibiting T- and B-cell development and proinflammatory cytokine release by monocytes and macrophages²⁶. It has also been used to successfully produce tolerance in a primate transplant model²⁷. However, five recipients of living donor kidneys were treated in this study, and all five developed early acute rejection, with biopsy characteristics similar to those seen in the alemtuzumab-alone study²⁵. Thus, even in combination with DSG, alemtuzumab does not induce tolerance in humans.

Alemtuzumab plus rituximab, MMF, and corticosteroids

This pilot study was published in abstract form at the World Transplant Congress in 2006. Thirty patients received alemtuzumab 30 mg on days 0 and 1 and rituximab 375 mg/m² on day 1, followed by MMF (1 g twice daily) and prednisolone (5-10 mg/d) as maintenance therapy²⁸. At nine months follow-up, patient and graft survival were 97 and 93%, respectively. The rejection rate was relatively high at 43%. Infection rates were also high, with a 23% incidence of cytomegalovirus (CMV) infection. These data also support the view that alemtuzumab should be used in combination with a calcineurin inhibitor.

Alemtuzumab at induction – non-randomized data

Alemtuzumab has been used with a variety of maintenance regimens and compared to a number of other immunosuppressive regimens in these non-randomized, retrospective studies (Table 2). These deficiencies, as well as widely differing maintenance regimens, make comparisons difficult, but we will at-

Table 2. Non-randomized studies of alemtuzumab as induction therapy

Study	Immunosuppression	Follow-up time (months)	(n)	Acute rejection at 1 year (%)	Infection (%)	CMV (%)	PTLD (%)	Auto-immunity
Watson, et al. ¹⁸	Low-dose cyclosporin monotherapy	60	33	20	30	3	3	Yes
Tan, et al. ²⁹	Low-dose tacrolimus monotherapy	16	205	6.8	1.5	0	0	No
Knechtle, et al. ³⁶	Calcineurin inhibitor + MMF	60	126	25	75	ND	0	No
Kauffman, et al. ³³	Low-dose tacrolimus + MMF	30	123	14.9	10.6	4	1.6	No
Shapiro, et al. ³⁴	Low-dose tacrolimus	18	90	17	ND	0	0	No
Shapiro, et al. (Pediatric study) ³⁵	Tacrolimus	22	9	0	0	0	0	Yes
Mital, et al. ³⁷	ND	12	50	ND	ND	ND	ND	ND

CMV: cytomegalovirus; PTLT: post-transplant lymphoproliferative disease; MMF: mycophenolate mofetil; ND: not documented.

tempt to categorize studies according to the regimen against which outcomes are compared.

Alemtuzumab versus “triple therapy”

Alemtuzumab induction followed by a low-dose calcineurin inhibitor has been compared with patients receiving so-called “triple therapy” in two studies. In the first from Cambridge, the “control group” received cyclosporin, azathioprine, and prednisolone¹⁸. In the second from Pittsburgh (USA), the control group received tacrolimus, MMF, and prednisolone²⁹.

Following the initial pilot study of 13 patients performed in Cambridge in 1997⁴, a further 20 patients were subsequently treated with two doses of alemtuzumab 20 mg on

days 0 and 1, and maintained on low-dose cyclosporin monotherapy (target trough level: 75-125 ng/ml). Data obtained at five-year follow-up were compared to a contemporaneous cohort treated with cyclosporin, azathioprine, and prednisolone¹⁸. There was no difference in graft survival and patient survival (79 and 88%, respectively, in the alemtuzumab group versus 74 and 83% in the control group), or in acute rejection rates (30% in the alemtuzumab group versus 27% in controls). Of note, episodes of acute rejection tended to occur much later in the alemtuzumab group (median time 170 days versus 21 days in controls). This has implications for post-transplant care, and requires continued vigilance in alemtuzumab-treated patients during the first year post-transplantation, particularly since by this time, many patients will have returned to a secondary care setting for follow-up. The overall incidence of infection in the alemtuzumab group was not significantly different to

that seen in the control group (30 vs. 19%). However, there was a 10-fold higher incidence of herpes zoster infections in the alemtuzumab group (15 vs. 1.5%). Two patients treated with alemtuzumab at induction in this study also developed autoimmune disease post-transplantation. One developed autoimmune hypothyroidism, and one an autoimmune hemolytic anemia, which was resistant to steroid therapy but responded to splenectomy. More recently, Kirk, et al. have also described a renal transplant recipient who developed Graves' disease four years post-alemtuzumab induction³⁰. The occurrence of autoimmune disease in association with alemtuzumab treatment was first described in patients with multiple sclerosis³¹. In this cohort of 57 patients, 28% of patients developed autoimmune thyroid disease, most of which was Graves' disease, with a single case of autoimmune hypothyroidism¹¹. Furthermore, in patients undergoing hematopoietic stem cell transplantation, the incidence of autoimmunity post-transplantation was found to be higher in patients who had received alemtuzumab pre-conditioning compared with those who had received anti-thymocyte globulin (16 vs. 1.9%)³². These cases were mostly autoimmune cytopenias. Although there are no other reports of autoimmunity in alemtuzumab-treated renal transplant recipients, this may be due to a reporting bias, as autoimmunity is not commonly a reported endpoint in transplant studies. Clinicians using alemtuzumab as induction therapy should be aware of the association with autoimmune diseases, particularly thyroid autoimmunity and cytopenias.

In the Pittsburgh study, 205 patients who had received a single dose of alemtuzumab 30 mg followed by low-dose tacrolimus monotherapy (target trough concentration: 10 ng/ml) were compared with a group of 47 historic controls who had received tacrolimus, MMF, and prednisolone²⁹. The mean follow-up in the alemtuzumab group was 493 days. Actuarial one-year patient

and graft survival were 98.6 and 98.1%, respectively, in the alemtuzumab group, compared to 93.6 and 91.5% in the control group. The incidence of acute rejection at one year was very low in the alemtuzumab group at 6.8% compared with 17% in the historic controls ($p < 0.05$) and the majority of these were mild, classified as Banff 1a or 1b. No major infectious complications were reported in this series and there were no cases of PTLD.

Alemtuzumab versus anti-CD25 induction

Kaufman, et al. in Chicago published a retrospective analysis of the long-term outcomes of renal transplant recipients who had received a single dose of alemtuzumab 30 mg ($n = 123$) or basiliximab ($n = 155$) at induction³³. Maintenance immunosuppression was the same for both groups and consisted of tacrolimus (target trough concentration: 6-8 ng/ml) and MMF, although the alemtuzumab group received a lower dose of MMF (1.5-2 vs. 2.5-3 g/d) and on average had lower tacrolimus levels. There was no difference in patient or graft survival and acute rejection rates at one year were equivalent (14.9% in the alemtuzumab group versus 13.5% in the basiliximab group). However, the kinetics of rejection was different, occurring much later in the alemtuzumab group (median 153 days) than in the basiliximab group (median 10 days). Major infection, including CMV, occurred at a similar frequency in both groups, as did malignancies.

Alemtuzumab versus thymoglobulin

Shapiro, et al. at Pittsburgh compared patients treated with thymoglobulin at induction ($n = 101$) or alemtuzumab 30 mg at induction ($n = 90$) with historic controls who had

received tacrolimus, prednisolone and MMF or sirolimus, without the use of an induction agent³⁴. Both the thymoglobulin and alemtuzumab groups received low-dose tacrolimus as maintenance therapy (target trough level: 10 ng/ml), which was space-weaned by lengthening the time between doses from 4-6 months onwards. At one year there was no difference in serum creatinine or in overall patient and graft survival. The rate of acute rejection at one year was also comparable at around 18% in both the alemtuzumab and thymoglobulin groups. This was significantly better than that seen in historic controls on triple therapy. As noted in other studies, acute rejection episodes tended to occur after six months in the alemtuzumab-treated patients. There were no episodes of CMV infection or PTLD.

The Pittsburgh group has also reported their experience using alemtuzumab induction in pediatric renal transplantation³⁵. Nine patients who had received alemtuzumab (0.4-0.5 mg/kg) were compared with eight historic controls who had received anti-thymocyte globulin (ATG). Both groups received tacrolimus maintenance therapy (target trough concentration: 10 ng/ml) which was space-weaned as described above. At a mean of 22 months follow-up there was no significant difference in patient or graft survival. There was a significant difference in the incidence of acute rejection, with no rejection episodes in the alemtuzumab group versus 14% rejection in the ATG group. Of note, one patient in both groups developed an autoimmune hemolytic anemia post-transplantation. In both cases this was responsive to corticosteroids.

Alemtuzumab versus thymoglobulin or CD25 induction

Knechtle, et al. compared 126 patients treated with alemtuzumab (30 mg on days 0

and 1) to 799 patients treated with a CD25 monoclonal antibody (basiliximab), 160 patients treated with thymoglobulin, and 156 patients treated with other therapies such as OKT3 and ATG³⁶. All patients received a calcineurin inhibitor, MMF, and prednisolone, except for the alemtuzumab group who were run steroid-free. At one year there was a significant difference in the incidence of acute rejection in favor of the alemtuzumab group ($p = 0.037$) and improved graft survival ($p = 0.016$). The reduction in acute rejection and improved graft survival was particularly impressive in patients with delayed graft function treated with alemtuzumab. There was no significant difference in patient survival. The authors raise the possibility that alemtuzumab induction therapy may be particularly helpful in patients with delayed graft function who are at increased risk of developing early acute rejection.

Mital, et al. carried out a retrospective review of 151 patients who had received a renal transplant at a single centre, comparing alemtuzumab induction with thymoglobulin or basiliximab³⁷. Brief details were presented in abstract form at the World Transplant Congress in 2006. At a minimum of nine months follow-up, acute rejection rates were said to be similar in all groups, but the authors were concerned about the high incidence of graft loss in alemtuzumab-treated patients, occurring in seven of 50 (14%), three of which were due to thrombosis, compared with 0 of 65 in the thymoglobulin cohort. The authors have therefore raised the concern that alemtuzumab may be associated with an increased risk of thrombosis, although this is not supported by other studies.

Alemtuzumab at induction – randomized trials

There are two randomized trials of alemtuzumab induction in the published lit-

Table 3. Randomized studies of alemtuzumab as induction therapy

Study	Immunosuppression	Follow-up (months)	(n)	Acute rejection at 1 year (%)	Infection (%)	CMV (%)	PTLD (%)	Auto-immunity
Ciancio, et al. ²⁴	Low-dose tacrolimus + MMF	18	30	16.6	20	0	–	No
Vathsala, et al. ³⁸	Low-dose cyclosporin monotherapy	6	20	25 (6 Mo)	135	45	0	No
Margareta, et al. ³⁹	Standard-dose tacrolimus monotherapy	6	65	16.8 (6 Mo)	0	0	0	No

CMV: cytomegalovirus; PTLT: post-transplant lymphoproliferative disease; MMF: mycophenolate mofetil; ND: not documented.

erature, and one in process, the preliminary results of which have been reported in abstract form (Table 3). We will discuss each in turn.

Ciancio, et al. undertook a randomized trial comparing three induction regimens in 90 patients undergoing their first cadaveric renal transplant²⁴. Thirty patients were randomized to each group and received thymoglobulin (1 mg/kg/d for one week), or alemtuzumab (0.3 mg/kg on days 0 and 4), or daclizumab (1 mg/kg on days 0, 14, 28, 42, and 56) at induction. Maintenance immunosuppression consisted of tacrolimus and MMF in all three arms, although the alemtuzumab group received half the dose of MMF (500 mg vs. 1 g twice daily) and had a lower target trough tacrolimus level (4-7 vs. 8-10 ng/ml). In addition, patients in the thymoglobulin and daclizumab groups received methyl prednisolone at induction and continued on maintenance corticosteroids, although in the final analysis 20% of the alemtuzumab group also required maintenance corticosteroids. Acute rejection rates at one year were equivalent in each group (16.6%), although there was a tendency for rejection to occur later in the alemtuzumab group. There was no difference in patient or graft survival or in renal function at one year. Infection rates were similar in all

three groups; 23% of patients in the thymoglobulin arm required hospitalization for infection, 20% in the alemtuzumab arm, and 13% in the daclizumab arm ($p = 0.6$). Interestingly, although patients who had received alemtuzumab had significantly more leukopenia, the proportion of T-cells with a possible regulatory phenotype was increased. The percentage of CD4+ T-cells that also stained brightly for CD25+ was around 12% preoperatively; on day 60 post-transplantation this had increased to 39% in alemtuzumab-treated patients compared with 22% in thymoglobulin-treated patients. Furthermore, when CD3+ T-cells were isolated from peripheral blood and FoxP3 mRNA levels assessed by rtPCR, there were double the number of FoxP3-positive cells in patients who had received alemtuzumab compared with thymoglobulin-treated patients²⁴.

The second randomized trial by Vathsala, et al. involved a multicentre trial comparing alemtuzumab induction therapy (20 mg on days 0 and 1) followed by maintenance cyclosporin (target trough level: 90-110 ng/ml) with the local “standard therapy”, a combination of cyclosporin (target trough level: 180-225 ng/ml), azathioprine (1 mg/kg), and corticosteroids³⁸. Numbers were small; 20 patients were recruited to the alem-

tuzumab arm (15 of which remained on a steroid-free maintenance regimen) and 10 patients to the “standard therapy” arm. At six months, patient and graft survival and serum creatinine were comparable as was the incidence of acute rejection (25% in the alemtuzumab group versus 20% in the “standard therapy” group). The incidence of infection was higher in alemtuzumab-treated patients, but this did not reach statistical significance³⁸. A relatively high number (45%) were said to have CMV infection, although most of these involved an asymptomatic increase in CMV titres. Although of interest, the data generated by this trial are limited by the small numbers of patients involved and the short follow-up time of just six months.

A third trial is underway in Germany and Austria, and an interim report was published in abstract form at the World Transplant Congress in 2006³⁹. Patients (n = 131) were randomized to receive alemtuzumab at induction (n = 65) followed by tacrolimus (trough level 8-12 ng/ml to six months, 5-8 ng/ml from six months onwards) or tacrolimus (trough levels as for alemtuzumab group), MMF (1-1.5 g), and corticosteroids (n = 66).

At six months, patient and graft survival and serum creatinine were equivalent in both groups, but the incidence of acute rejection was significantly lower in the alemtuzumab group (17 vs. 36%; p = 0.0012). There was no difference in infection rates.

Conclusions

Analysis of the available data allows a number of conclusions to be drawn with regards to the use of alemtuzumab as induction therapy:

- Alemtuzumab does not induce tolerance when used as monotherapy, although it may be pro-tolerogenic, skewing T-cell sub-

sets towards an excess with a regulatory phenotype.

- Alemtuzumab must be used in combination with a calcineurin inhibitor, at least initially. When used in combination with sirolimus or sirolimus and MMF, rates of early acute rejection were high, particularly humoral rejection.

- When used in combination with low-dose CNI maintenance, alemtuzumab gives low rates of acute rejection, at least comparable to anti-CD25 induction therapy. Overall, the data we have reviewed using alemtuzumab plus a calcineurin inhibitor with or without MMF suggests a mean incidence of acute rejection of 14% at one year. Its use may be particularly desirable in patients with delayed graft function, as seen in a high proportion of patients receiving asystolic grafts.

- Acute rejection episodes occur late; this may have implications on post-transplant monitoring, and in the distribution of cost for post-transplant care.

- Alemtuzumab at induction does not appear to be associated with an excess increased risk of serious infection. In our review of available studies, the overall incidence of infection was 37% (range 0-135%), many of which were minor infections such as urinary tract infections. The wide range may relate to accuracy of reporting or differences in concurrent maintenance immunosuppressants used. The incidence of CMV infection was 6%. We conclude that alemtuzumab does not incur an increased risk of infection if used with an appropriate maintenance regimen. This view is supported by recent data examining the incidence of infection in all patients who had received alemtuzumab in solid organ transplantation (both at induction and for the treatment of acute rejection) including liver, kidney, heart lung, pancreas, intestinal and multivisceral

transplants. Of 547 patients treated, only 10% developed opportunistic infections, including 2.9% of which were CMV disease. Of interest, patients who had received alemtuzumab for induction were less likely to develop infection (4.5 vs. 21%)⁴⁰. Similarly, in another U.S. series, a 16% overall rate of infection was reported in 49 renal transplant patients post-alemtuzumab induction with a 6% incidence of CMV disease⁴¹. The relatively low incidence of CMV infection may be offset by an increase in other herpesvirus infections in alemtuzumab-treated patients.

– Alemtuzumab does not appear to be associated with an increased incidence of PTLD. In our review of the published studies of alemtuzumab as induction therapy, the overall incidence is low at 0.3%. Our conclusion is supported by the data reported by Peleg, et al. in the patients treated with alemtuzumab for a variety of organ transplants, where the overall incidence of PTLD was 0.9%⁴⁰.

– Alemtuzumab may be associated with the development of autoimmune disease, particularly autoimmune thyroid disease and cytopenias.

– Alemtuzumab may be associated with an increased risk of early graft thrombosis.

With these caveats in mind, current data suggests that alemtuzumab is a promising induction agent, and we look forward to the availability of long-term, appropriately powered, randomized studies to further guide our optimal use of this powerful agent.

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