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Alefacept Treatment in the Setting of Transplantation

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Abstract

Alefacept is a dimeric human fusion protein that consists of the CD2-binding portion of leukocyte-function antigen-3 linked to the crystallizable fragment region of immunoglobulin G1. Alefacept exerts its action via dose-dependent depletion of memory T-cells by apoptosis and inhibits T-cell activation. Alefacept has been approved by the Food and Drug Administration to treat adults with moderate-to-severe chronic plaque psoriasis. It has also been used off-label in the setting of refractory acute or chronic graft-versus-host disease. More recently, two phase II studies have been conducted on de novo primary kidney transplant patients. In these studies, maintenance immunosuppression relied on tacrolimus and steroids, with or without mycophenolate mofetil in one of them. Alefacept (or placebo) was then given as an adjunct induction drug within the first 12 weeks posttransplantation. Compared to the placebo, alefacept did not significantly decrease the rate of biopsy-proven acute rejection within the first six months posttransplantation, although the absolute number of circulatory memory T-cells was significantly decreased. However, in 2011 the sponsor Astellas decided to stop the development of alefacept in the setting of kidney transplantation. This is a pity because alefacept may have been of potential benefit to sensitized patients in whom the blockade of memory cells is of utmost importance. **(Trends in Transplant. 2014;8:35-40)**

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Key words

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Introduction

Alefacept is a dimeric human fusion protein that consists of the CD2-binding portion of leukocyte function antigen-3 linked to the crystallizable fragment (Fc) region of immunoglobulin G1 (IgG1)[1]. Alefacept exerts its action via dose-dependent depletion of memory T-cells by apoptosis and inhibits T-cell activation[1,2]. Alefacept was the first biological therapy approved by the Food and Drug Administration (in January 2003) to treat adults with moderate-to-severe chronic plaque psoriasis and who are candidates for systemic therapy or phototherapy. In this review we examine the clinical situations in which alefacept has been used, namely dermatology, but also bone marrow and kidney transplantation.

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Dermatology

Alefacept has been shown to be effective as monotherapy for chronic plaque psoriasis in several clinical studies[3]. In a phase II, multicenter, randomized controlled trial, 229 patients received one of three doses of intravenous (IV) alefacept (0.025, 0.075, or 0.15 mg/kg body weight), or a placebo control. Treatment was for 12 weeks, with a follow-up period of 12 weeks posttreatment. It was shown that the Psoriasis-Area Severity Index was improved by 38-53% in patients that received alefacept compared to 21% improvement in the placebo group[4]. Moreover, under alefacept treatment, improvement was correlated with a reduced number of memory effector T-lymphocytes. Subsequent phase III trials have demonstrated improved clinical efficacy and tolerability in patients receiving two 12-week courses of IV alefacept therapy[1,5]. Intramuscular alefacept administrated as a once-weekly injection of 10 or 15 mg for 12 weeks was proven to be similarly safe and effective in improving chronic plaque psoriasis[6].

To date no randomized controlled trials have directly compared the efficacy of alefacept with other biologics approved for treating psoriasis. However, a meta-analysis examined the efficacy of four biological agents: alefacept, efalizumab, etanercept, and infliximab. Alefacept was found to be the least effective of the agents studied[7]. Recently, Mikhael, et al. performed a cost-comparison analysis of various psoriasis treatments: they found that for a 60 kg patient, alefacept administered in two 12-week courses was the most costly therapy, followed by infliximab[8]. In addition, alefacept as a monotherapy failed to treat vitiligo[9].

Bone marrow transplantation

In a preliminary report, Shapira. et al. reported on seven bone marrow transplant patients with steroid-resistant/dependent acute graft-versus-host disease (GVHD) who were given between four and 16 doses of alefacept at similar dosages to those given to psoriasis patients[10]. All seven patients responded: three patients had a full response, whereas the other four had a partial response. There were no immediate alefacept-related side effects. Three patients had later cytomegalovirus reactivation after receiving alefacept. More recently, the authors reported on 16 other patients with acute steroid-resistant/dependent GVHD treated with alefacept[11]. Dosage was much more intensive for these patients compared to those in the previous study: i.e., alefacept was given intramuscularly at 15 mg daily for seven consecutive days followed by a biweekly 15 mg maintenance treatment if needed. They found that 13 of the 16 patients showed a response: a complete response for skin GVHD was observed in 10 patients, three out of nine patients with gastrointestinal GVHD showed a complete response, and three out of six patients with liver GVHD had a complete response. All the responses were durable and allowed the daily steroid dose to be reduced significantly.

The same authors have reported on patients receiving alefacept therapy in the setting of refractory chronic extensive GVHD[12]. In this instance, 12 patients were included, of whom eight, i.e. 9 of 13 episodes showed a response. The median time to a response was 2.25 weeks: responses were marked (n = 3), moderate (n = 2), or minimal (n = 4). In two of the responding patients, the response was only temporary. After a median follow-up of 30 months, six of the 12 patients were alive and all but one had stable or improved chronic GVHD. The authors also observed a significant reduction in memory T-cells ($CD45RO^+$) compared with naive ($CD45RA^+$) T-cells in all patients. These preliminary results of the use of alefacept therapy to treat acute or chronic GVHD have not been investigated further.

Of note, Stotler, et al. reported a case of a liver transplant recipient who developed cutaneous grade 2/3 GVHD associated with pancytopenia at 27 days posttransplantation. Peripheral blood DNA showed mixed chimerism (11%, donor DNA) and T-cell-enriched factors (81%, donor DNA), confirming a diagnosis of GVHD[12]. He was treated with 30 mg of alefacept followed by three additional doses of 30 mg every three days: both cutaneous lesions and pancytopenia were cured within a few days[13].

Organ transplantation

Alefacept has been used in nonhuman primate kidney transplantation models as well as in human kidney transplantation. Blockade of the CD28/B7 co-stimulatory pathway has been suggested as a means of preventing allograft rejection without the side effects of calcineurin inhibitors; indeed, the CD28/B7-specific fusion protein CTLA4-Ig has been shown to induce permanent engraftment of allografts in some rodent models, particularly when combined with the drug sirolimus and/or donor-specific transfusion[14].

Several mechanisms that occur within co-stimulation, blockade-resistant rejection have been demonstrated experimentally, which show that many implicated T-cells have a memory phenotype (T_{EM}-cells)[15]. Thus, it is of interest to have adjuvant therapies that can transiently but specifically neutralize memory T-cells. Hence, Weaver, et al. investigated whether alefacept could be used as an adjuvant therapy in association with a co-stimulation blockade, i.e., CTLA4-Ig, sirolimus, and/or donor-specific transfusion, in a nonhuman primate model of kidney transplantation[16]. Renal allograft rhesus monkeys were treated with alefacept and/or CTLA4-Ig weekly for eight weeks, oral sirolimus daily for 90 days, and pretransplant whole-blood donor-specific transfusions (DST). They found that animals that received no treatment, sirolimus alone, sirolimus with DST, sirolimus with DST and CTLA4-Ig, or sirolimus with DST and alefacept had progressively increased survival; however, no animals remained rejection-free beyond their treatment period[16]. All animals developed alloantibodies by the onset of rejection. Conversely, when both alefacept and CTLA4-Ig were combined with sirolimus, with or without DST, significantly prolonged survival was seen compared to all other groups. Moreover, these animals remained rejection-free beyond the period of treatment (> 90 days).

This study demonstrated that alefacept was additive to the co-stimulation blockade-based regimen. In these animals, alefacept therapy was associated with modest decreases in total lymphocyte counts, with a greater reduction in $CD8^+$ cells and an increase in the CD4/CD8 ratio, which was reversed after the withdrawal of alefacept. In addition, they observed that alefacept therapy was associated with selective depletion of T_{EM}-cells without any alteration to the numbers of naive T-cells; in particular, the greatest depletion was seen without the T-effector (T_{EM}; $CD28^-$ $CD95^+$) subset of $CD4^+$ and $CD8^+$ T-cells. The T_{EM} counts were markedly reduced after three weeks of alefacept therapy. At the time of rejection, T_{EM} counts in alefacept-treated animals had returned to normal. Mechanistically, alefacept appeared to increase CD2 density in alloresponse cells, particularly $CD28^-$ T_{EM} cells, which are the least susceptible to co-stimulation blockade and are the most alloresponsive. Hence, alefacept targets co-stimulation blockade-resistant alloreactive effector memory T-cells, particularly those that are $CD2^{high}$ and $CD8^-$[17,18]. It also significantly reduces circulating memory and effector T-cell populations[4,19].

Recently, Lee et al. reported that alefacept promotes immunosuppression-free renal allograft survival in nonhuman primates via depletion of recipient memory T-cells[20]. In this

kidney transplant model they developed a strategy of "delayed tolerance induction" in which recipients initially underwent kidney transplantation with conventional immunosuppression and then received conditioning and a bone marrow transplant from the kidney donor four months later. In this setting they observed that additional treatment with an anti-CD8 mAb effectively prevented the expansion/activation of donor-reactive $CD8^+$ memory T-cells post-bone marrow transplant and allowed mixed chimerism induction and long-term acceptance of kidney allografts. However, this was associated with (i) long-lasting depletion of $CD8^+$ T- and natural killer (NK) cells, (ii) no promotion of chimerism and allograft tolerance, and (iii) a high incidence of viral infection and Epstein Barr virus-related lymphomas. Lee, et al. found in this model that alefacept (at 1 mg/kg bodyweight) given to bone marrow transplant patients on days –1, 5, 12, and 19, (i) significantly delayed the expansion of $CD2^{high}$ cells, including $CD8^+$ memory T-cells, while sparing naive $CD8^+$ T- and NK cells, and (ii) achieved mixed chimerism and long-term immunosuppression-free renal allograft survival, with no increase in infection or lymphoma rates[20].

In humans, so far, only two phase II studies have been conducted, and both have involved *de novo* kidney transplant recipients where alefacept therapy was added to the conventional immunosuppression therapy, with or without an induction therapy[21,22]. The first phase II study[21] was conducted in Europe, while the second was conducted in the USA[22].

The first study evaluated the efficacy and safety of alefacept compared to a placebo in a double-blind study when administered in combination with a standard-of-care immunosuppressive regimen (tacrolimus, mycophenolate mofetil, and steroids). The study included adult recipients of a primary renal transplant, or a re-transplant from a non-HLA-identical living donor, or a transplant from a deceased donor aged between five and 59 years with a compatible ABO blood type. Recipients who had pretransplant panel-reactive antibody levels > 20% were excluded, as were those that had received a kidney from an expanded-criteria donor, or from a cardiac death donor, or if cold ischemia time was > 30 hours. The first dose of alefacept (n = 105 patients) or placebo (n = 107 patients) of 7.5 mg was given intra-operatively as an IV bolus prior to reperfusion. A second bolus of alefacept (7.5 mg IV) was administered on day 3, with subsequent 15 mg doses of alefacept given weekly as subcutaneous injections for 12 weeks. The same dose and schedule was applied to the placebo arm, in which a saline solution was administered. Adjuvant immunosuppression was based on tacrolimus (0.2 mg/kg/day) to maintain whole-blood trough levels of 10-20 ng/ml (days 0-28), then 7-16 ng/ml of tacrolimus (days 29-90), and then 5-15 ng/ml (day 90 onwards). In addition, mycophenolate mofetil (MMF) was given at 750 mg twice daily, plus steroids, which were reduced to 5-10 mg/day by day 61 onwards.

In this European phase II study, the primary endpoint was the rate of biopsy-confirmed acute T-cell mediated rejections (Banff grade ≥ 1) up until month 6; this rate was not statistically different between the alefacept- and placebo-treatment groups (11 vs. 7%; p = 0.309). All the rejection episodes occurred within the first seven weeks post-transplantation and the majority occurred in the first two weeks. Grade I and II antibody-mediated rejections occurred in 3.8% of the alefacept group and in 2.8% of placebo-treated patients (p = 0.696). In addition there were no statistically significant differences between the treatment groups regarding any of the secondary efficacy endpoints, including rejection, anti-lymphocyte antibody therapy given for rejection and graft survival, graft loss, delayed-graft function, or efficacy failure. Throughout the study, with regards to T-lymphocyte

subset counts, there were no significant differences in the mean counts of $CD4^+$ $CD45RA^+$ and $CD8^+$ $CD45RA^+$ cells, i.e., naive T-cells. Conversely, with regards to $CD4^+$ $CD45RO^+$ cells, i.e., memory T-cells, from week 3 to month 6, the mean counts were significantly lower in the alefacept group compared to the placebo group. Similar results were observed for the $CD8^+$ $CD45RO^+$ counts. Renal function was similar in both groups for the duration of the study. Adverse events (AE), treatment-related AE, serious AE, and treatment-related serious AE occurred with a similar frequency in the two treatment groups. The overall incidence of malignancies was higher in the alefacept group compared to the placebo group (5.7 vs. 0.9%; $p = 0.06$). However, most of the malignancies were possibly/probably present at the time of transplantation. Finally, there were four deaths in the study: one in the alefacept group and three in the placebo group.

The second phase II trial was conducted in North America[22] and was a randomized, open-label, multicenter study that included 309 *de novo* adult kidney transplant recipients. Its design varied from the European study in that it aimed to minimize tacrolimus or MMF and assessed the effect of alefacept on biopsy-proven acute rejection at six months. In this study, the control arm (n = 79) received basiliximab as an induction therapy (day 0 and 4) and then full-dose tacrolimus, which aimed at trough levels of 10-20 ng/ml by day 28, plus MMF and steroids. The three experimental arms received 7.5 mg of alefacept (IV) on day 0 and 3. In one arm (n = 77), tacrolimus was reduced to trough levels of 3-7 ng/ml from day 0 to 28, in association with MMF, steroids, and alefacept (at 15 mg subcutaneously) on day 7, and then weekly for 12 weeks. In the second arm, MMF was omitted (n = 75), the patients were placed on steroids, full doses of tacrolimus were given with trough levels of 10-20 ng/ml from day 0 to 28, in association with alefacept at 15 mg subcutaneously on day 7, and then weekly for 12 weeks. In the third experimental arm (n = 78), the patients received MMF, steroids, low doses of tacrolimus (trough levels 3-7 ng/ml from day 0 to 28), and alefacept at 30 mg on day 7, and then 30 mg every other week for 12 weeks. Thereafter, the three treatment groups received additional alefacept injections subcutaneously in months 4, 5, and 6. The primary endpoint was the incidence of biopsy-proven acute rejection at six months. The non-inferiority margin was 10%.

Patients were comparable with regards to all baseline characteristics. At the end of the study period (six months), patient and graft survival rates, as well as kidney allograft function, did not vary statistically across the four groups. The primary endpoint occurred in 12.7% of the control patients compared to 26.3% ($p < 0.05$) in the low-dose tacrolimus arm, 18.8% in the MMF-omitted arm, and 16.7% in the group that received 30 mg of alefacept. Posttransplant $CD4^+$ memory T-cells and $CD8^+$ memory T-cells became significantly lower in the alefacept arms compared to the control arm. Infection rates, e.g. cytomegalovirus, as well as malignancy rates, did not vary significantly across the four arms.

After publication of these two negative trials, with the results that the addition of alefacept as an induction therapy to *de novo* primary kidney transplant recipients did not significantly decrease the rate of biopsy-proven acute rejection by six months posttransplantation, the pharmaceutical company Astellas decided to stop its development of this drug in the setting of kidney transplantation. This is a pity because alefacept may have been of potential benefit to sensitized patients in whom the blockade of memory cells is of utmost importance.

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