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CONCISE COMMUNICATION

Alefacept therapy produces remission for patients with chronic plaque psoriasis

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Summary

Background Alefacept, human LFA-3/IgG_1 fusion protein, is a novel biological agent currently being developed for the treatment of chronic plaque psoriasis. Alefacept selectively reduces the memory-effector T cells that have been implicated in the pathogenesis of the disease; as a result, alefacept is classified as a therapy that induces remission (so-called 'remittive' therapy). In a previously published randomized, placebo-controlled phase II study of intravenous alefacept in 229 patients with chronic plaque psoriasis, clinical improvement was observed during dosing as well as in the postdosing follow-up period.

Objectives To assess the remission period following alefacept therapy.

Methods The time before re-treatment was required was measured in patients who were 'clear' or 'almost clear' of disease according to a physician global assessment at the end of the follow-up phase.

Results In these patients, responses were sustained for a median of 10 months, and for up to 18 months. No patient reported disease rebound after cessation of alefacept.

Conclusions Alefacept is a biological agent for the treatment of chronic plaque psoriasis that provides disease-free intervals and time off drug therapy.

Keywords: alefacept, disease remission, duration of response, psoriasis

Currently available systemic therapies for chronic plaque psoriasis are primarily suppressive in nature. They can produce clinical improvement to clearing during therapy, but responses are typically of short duration and may be accompanied by disease rebound after therapy is withdrawn. Ciclosporin is an example of a drug in which maintenance therapy is necessary to sustain a favourable response,[1] and there have been reports of disease rebound or worsening after treatment is stopped.[2,3] In addition to the constant requirement for drug therapy, patients receiving these suppressive agents (e.g. ciclosporin, methotrexate) are at risk for organ toxicities, such as nephrotoxicity and hepatotoxicity.[4–6]

Therapies that provide long-lasting remission of psoriasis are characterized by mechanisms that reduce T cells in skin lesions.[7] Psoralen plus long-wave ultraviolet (UV) radiation (PUVA), and perhaps UVB, are the only currently available treatments for psoriasis that produce a meaningful remission of disease after therapy is complete.[8,9] For PUVA, this effect has been associated with a significant reduction of tissue-infiltrating lymphocytes in psoriatic skin.[10,11] However, repeated and long-term use of phototherapy is

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associated with an increased risk of skin cancer.[12–14] The limitations of current therapies highlight the need for safe therapies for psoriasis that increase disease-free intervals and time off toxic treatments.

Alefacept (currently being developed under the trade name Amevive®; Biogen Inc., Cambridge, MA, U.S.A.) is a novel and selective biological agent. It is a fully human LFA-3/IgG_1 fusion protein that binds CD2 receptors expressed on the surface of T cells and natural killer (NK) cells.[15] CD2 expression is higher on memory-effector (expressing CD45RO+ markers) CD4+ and CD8+ T cells, which have been strongly implicated in the pathogenesis of psoriasis,[16,17] compared with naïve T cells that do not express CD45RO.[18,19] By blocking the LFA-3/CD2 interaction on T cells, alefacept selectively inhibits T-cell activation and proliferation.[15,20] In addition, the Fc portion of alefacept interacts with the immunoglobulin receptor FcγRIII on the surface of NK cells, resulting in NK-cell-induced T-cell apoptosis.[21] *In vivo*, alefacept selectively reduces circulating memory T cells, which parallels its potential to induce remission in psoriasis.[20,22]

In a phase II study of alefacept therapy,[22] many patients showed continued improvement after cessation of treatment. This finding suggested that assessment of clinical efficacy at one time point does not fully reflect the percentage of patients who respond to alefacept; thus, response rates were determined over the entire study period. In addition, to quantify the remission provided by alefacept, the time before patients required further alefacept therapy was evaluated.

Patients and methods

Alefacept was tested in a randomized, multicentre, double-blind, placebo-controlled, parallel-group, phase II study; a detailed description has been published previously.[22] In brief, patients aged 18–70 years with chronic plaque psoriasis (body surface involvement ≥ 10%, duration of psoriasis > 12 months before entry, and prior systemic treatment or phototherapy or candidates for such therapy) were randomized to receive alefacept 0·025, 0·075 or 0·150 mg kg^{-1} or placebo administered as a 30-s intravenous bolus injection once weekly for 12 weeks. Systemic therapies, phototherapy or potent topical therapies were not allowed from 4 weeks before treatment through the second week after alefacept was discontinued. For psoriasis of the groin, scalp, palm or soles only, moderate potency topical corticosteroids, keratolytics, coal tar or calcipotriol could be used if necessary. Emollients could be used elsewhere if symptoms warranted, but not within 12 h of physician evaluation. The institutional review board at each institution approved the protocol and all patients provided written informed consent.

Efficacy was measured by changes in Psoriasis Area and Severity Index (PASI) from baseline and an overall assessment of disease severity, the physician global assessment (PGA), in which the treating physician rated the extent of psoriatic involvement at each visit on a seven-point scale: 0, clear (no psoriasis); 1, almost clear; 2, mild; 3, mild to moderate; 4, moderate; 5, moderate to severe; 6, severe. Patients who completed the 12-week treatment and 12-week follow-up periods were eligible to receive subsequent courses of alefacept. Re-treatment with alefacept was initiated when a patient's disease had progressed such that the attending physician and the patient felt that systemic therapy was required. The time to re-treatment was recorded as the time from the last dose of alefacept in the phase II study until further systemic treatment with alefacept was initiated.

Results

In total, 229 patients were enrolled in the phase II study (59, 57, 55 and 58 in the placebo, 0·025 mg kg^{-1} alefacept, 0·075 mg kg^{-1} alefacept and 0·150 mg kg^{-1} alefacept groups, respectively), the results of which have been published previously.[22] Baseline demographics and clinical characteristics were similar among all treatment groups.[22,23]

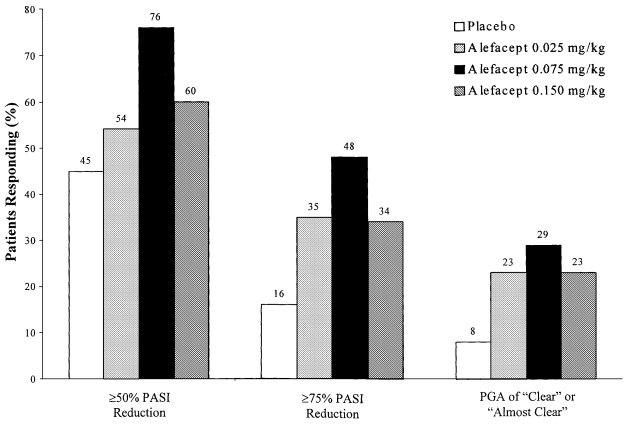

Figure 1. Overall response rates: percentage of patients achieving response criteria over the entire study period ($P < 0·001$ for the overall treatment difference for each of the three response criteria, logistic regression). PASI, Psoriasis Area and Severity Index; PGA, physician global assessment.

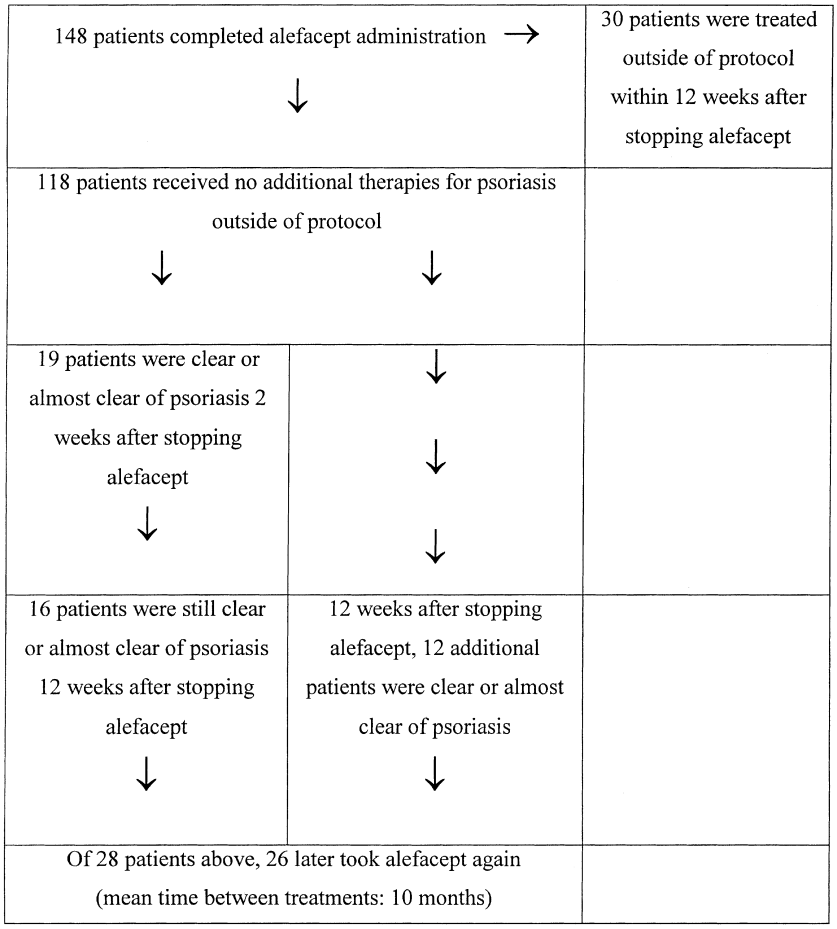

Figure 2. Flow chart of patients who obtained remissions with alefacept therapy.

Of the 229 patients, 197 completed the study. The most common reasons for discontinuing treatment were worsening of disease and voluntary withdrawal in the placebo group (17% of patients receiving placebo) and voluntary withdrawal, being lost to follow-up, and adverse events in the three alefacept groups combined (13% of patients receiving alefacept).[22] Alefacept was well tolerated and adverse events were generally mild. The most common adverse events were pharyngitis, headache, accidental injury, rhinitis and dizziness.[22] Laboratory tests showed no consistent chemical abnormalities in any group.

Two weeks after treatment, the mean reduction in PASI was 21% in the placebo group and 38%, 53% and 53% in the 0·025 mg kg^{-1}, 0·075 mg kg^{-1} and 0·150 mg kg^{-1} alefacept groups, respectively.[22] Overall response rates are shown in Figure 1. At the most effective dose (0·075 mg kg^{-1}), three-quarters of patients achieved a 50% or greater reduction in PASI, approximately half achieved a 75% or greater reduction in PASI, and nearly one-third were 'clear' or 'almost clear' according to the PGA.

Of 148 patients who were assigned to and completed alefacept therapy, 118 (80%) achieved sufficient improvement that they required no added therapy for psoriasis during the initial 12-week post-treatment follow-up (Fig. 2).[22] Two weeks after treatment, 19 of these patients (16%) were determined to be 'clear' or 'almost clear' of psoriasis by the PGA, with 16 of the 19 patients (84%) maintaining this level of response during the 12-week follow-up period. Twelve additional patients showed continued improvement after dosing was stopped and, despite having had no additional psoriasis treatment, they became 'clear' or 'almost clear' of disease during the 12-week follow-up, giving a total of 28 patients (24%).[22] Of these 28 patients, 26 went on to participate in a subsequent open-label study; this group of patients did not require further systemic therapy with alefacept for a median of 10 months (range 6–18).[22] There was no correlation

Table 1. Mean ± SD length of remission in three groups of alefacept-treated patients

Dose (mg kg^{-1})	*n*	Length of remission (days)
0·025	8	291 ± 108
0·075	9	338 ± 128
0·150	9	377 ± 92

The correlation between assigned dose and length of remission was not statistically significant ($P = 0{\cdot}28$).

between dose of alefacept and length of remission ($P = 0{\cdot}28$, Table 1). Additional courses of alefacept also provided similar periods of remission.[24] There have been no reports of rapid flares or rebound of psoriasis after cessation of alefacept therapy.[22,24]

Discussion

Alefacept, administered once weekly for 12 weeks, is an effective and well-tolerated agent for patients with chronic plaque psoriasis.[22] Patients showed continued improvement in psoriasis after the end of the 12-week treatment course, with substantial improvements in both PASI scores and PGA over the entire study period. Importantly, these responses were sustained without the need for re-treatment with alefacept for up to 18 months in some patients.

Unfortunately, the duration of response for currently available antipsoriatic therapies is not well defined and has not been reported routinely.[8] The time to re-treatment reported herein provides an estimate of what would be expected to happen in clinical practice because it is based on both the clinician's and the patient's appreciation of disease severity and need for re-treatment.

A review conducted by Koo and Lebwohl[8] indicated that the average duration of response with ciclosporin is approximately 6 weeks and the median time to relapse with methotrexate is approximately 10 weeks. As a result, most patients are rarely free of disease, which continues to place them at risk for adverse events from drug therapy. Furthermore, withdrawal of these generalized immunosuppressants has been associated occasionally with rapid disease flares or conversion of disease to more severe forms, such as pustular or erythrodermic psoriasis, which can be life-threatening.[2,3,25]

Among patients who achieve clearing or near-clearing of their psoriasis, the 10-month median time to re-treatment observed with alefacept is markedly longer than what we typically have observed in our patients using traditional systemic therapies for psoriasis (e.g. ciclosporin, methotrexate). The durable responses in patients treated with alefacept are similar to those we have observed in some patients after PUVA therapy. In one long-term study, patients treated with PUVA were without recurrence for 64 weeks.[8] This sustained effect has been linked to a cytotoxic action of PUVA on activated lymphocytes in lesional skin.[10,11] Alefacept also depletes lymphocytes, but in a selective way, by removing mainly memory T cells.

Further evaluations of response duration are warranted and were incorporated into the design of large, randomized, placebo-controlled phase III studies of alefacept. In these studies, patients who had at least a 75% improvement in their PASI scores were considered to be in remission until they had relapsed to a 50% improvement in PASI. The phase III results of alefacept therapy for psoriasis[26,27] support those found in this study, namely that alefacept provides a long-term remission of more than 7 months, consistent with its mechanism of action in selectively depleting memory-effector T cells.[7,21,22]

Note added in proof

In January 2003, alefacept was licensed by the US Food and Drug Administration as Amevive.

References

1 Ellis CN, Fradin MS, Messana JM *et al.* Cyclosporine for plaque-type psoriasis. Results of a multidose, double-blind trial. *N Engl J Med* 1991; **324**: 277–84.
2 Higgins E, Munro C, Friedmann PS *et al.* Risk of relapse upon withdrawal of cyclosporin therapy for psoriasis. *Lancet* 1988; **ii**: 802–3.
3 Georgala S, Koumantaki E, Rallis E *et al.* Generalized pustular psoriasis developing during withdrawal of long-term cyclosporin therapy. *Br J Dermatol* 2000; **142**: 1057–8.
4 Lim KK, Su WP, Schroeter AL *et al.* Cyclosporine in the treatment of dermatological disease: an update. *Mayo Clin Proc* 1996; **71**: 1182–91.
5 Messana JM, Johnson KJ, Mihatsch MJ *et al.* Renal structure and function effects after low dose cyclosporine in psoriasis patients: a preliminary report. *Clin Nephrol* 1995; **43**: 150–3.
6 Themido R, Loureiro M, Pecegueiro M *et al.* Methotrexate hepatotoxicity in psoriatic patients submitted to long-term therapy. *Acta Derm Venereol (Stockh)* 1992; **72**: 361–4.
7 Singri P, West DP, Gordon KB. Biologic therapy for psoriasis: the new therapeutic frontier. *Arch Dermatol* 2002; **138**: 657–63.
8 Koo J, Lebwohl M. Duration of remission of psoriasis therapies. *J Am Acad Dermatol* 1999; **41**: 51–9.
9 Walters IB, Burack LH, Coven TR *et al.* Suberythemogenic narrow-band UVB is markedly more effective than conventional UVB in treatment of psoriasis vulgaris. *J Am Acad Dermatol* 1999; **40**: 893–900.

10 Coven TR, Murphy FP, Gilleaudeau P *et al.* Trimethylpsoralen bath PUVA is a remittive treatment for psoriasis vulgaris. *Arch Dermatol* 1998; **134**: 1263–8.
11 Vallat VP, Gilleaudeau P, Battat L *et al.* PUVA bath therapy strongly suppresses immunological and epidermal activation in psoriasis: a possible cellular basis for remittive therapy. *J Exp Med* 1994; **180**: 283–96.
12 Lindelof B, Sigurgeirsson B, Tegner E *et al.* PUVA and cancer risk: the Swedish follow-up study. *Br J Dermatol* 1999; **141**: 108–12.
13 Shephard SE, Panizzon RG. Carcinogenic risk of bath PUVA in comparison to oral PUVA therapy. *Dermatology* 1999; **199**: 106–12.
14 Stern RS and the PUVA Follow up Study. The risk of melanoma in association with long-term exposure to PUVA. *J Am Acad Dermatol* 2001; **44**: 755–61.
15 Miller GT, Hochman PS, Meier W *et al.* Specific interaction of lymphocyte function-associated antigen 3 with CD2 can inhibit T-cell responses. *J Exp Med* 1993; **178**: 211–22.
16 Austin LM, Ozawa M, Kikuchi T *et al.* The majority of epidermal T cells in psoriasis vulgaris lesions can produce type 1 cytokines, interferon-γ, interleukin-2, and tumor necrosis factor-α, defining TC1 (cytotoxic T lymphocyte) and TH1 effector populations: a type 1 differentiation bias is also measured in circulating blood T cells in psoriatic patients. *J Invest Dermatol* 1999; **113**: 752–9.
17 Friedrich M, Krammig S, Henze M *et al.* Flow cytometric characterization of lesional T cells in psoriasis: intracellular cytokine and surface antigen expression indicates an activated, memory/effector type 1 immunophenotype. *Arch Dermatol Res* 2000; **292**: 519–21.
18 Sanders ME, Makgoba MW, Sharrow SO *et al.* Human memory T lymphocytes express increased levels of three cell adhesion molecules (LFA-3, CD2, and LFA-1) and three other molecules (UCHL1, CDw29, and Pgp-1) and have enhanced IFN-γ production. *J Immunol* 1988; **140**: 1401–7.
19 Majeau GR, Whitty A, Yim K *et al.* Low affinity binding of an LFA-3/IgG1 fusion protein to $CD2^+$ T cells is independent of cell activation. *Cell Adhes Commun* 1999; **7**: 267–9.
20 Chisholm PL, Williams CA, Jones WE *et al.* The effects of an immunomodulatory LFA3-IgG_1 fusion protein on nonhuman primates. *Ther Immunol* 1994; **1**: 205–16.
21 Majeau GR, Meier W, Jimmo B *et al.* Mechanism of lymphocyte function-associated molecule 3-Ig fusion proteins inhibition of T-cell responses. Structure/function analysis *in vitro* and in human CD2 transgenic mice. *J Immunol* 1994; **152**: 2753–67.
22 Ellis CN, Krueger GG, for the Alefacept Clinical Study Group. Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. *N Engl J Med* 2001; **345**: 248–55.
23 Millard TP, Birch KE, Young ER. Treatment of plaque psoriasis. *N Engl J Med* 2001; **345**: 1853–4 (Letter).
24 Ellis CN, Krueger G, Shrager D. Repeated courses of alefacept therapy in chronic plaque psoriasis provide consistent efficacy and safety. *J Eur Acad Dermatol Venereol* 2001; **15**: 246 (Abstr.).
25 Cacoub P, Artru L, Canesi M *et al.* Life-threatening psoriasis relapse on withdrawal of cyclosporine. *Lancet* 1988; **ii**: 219–20.
26 Amevive® (alefacept) briefing document. Food and Drug Administration web site. Available at: http://www.fda.gov/ohrms/dockets/ac/02/briefing/3865B1_01_Biogen.pdf. Accessed 27 May, 2002.
27 Krueger GG, Papp KA, Stough DB *et al.* for the Alefacept Clinical Study Group. A randomized, double-blind, placebo-controlled phase III study evaluating efficacy and tolerability of 2 courses of alefacept in patients with chronic plaque psoriasis. *J Am Acad Dermatol* 2002; **47**: 821–33.