REPORT

Alefacept for psoriasis and psoriatic arthritis

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Ann Rheum Dis 2005;**64**:iv58–iv60. doi: 10.1136/ard.2005.042655

Alefacept is a bioengineered fusion protein of soluble lymphocyte function antigen (LFA-3) with Fc fragments of IgG1. It is marketed in many countries for the treatment of moderate to severe psoriasis. This paper reviews the data supporting the use of alefacept in psoriasis and psoriatic arthritis.

Alefacept is a bioengineered fusion protein of soluble Lymphocyte Function Antigen (LFA-3)¹ with Fc fragments of IgG1. It is marketed in the USA, Australia, Canada, Argentina, Switzerland, Kuwait, and Israel as monotherapy for the treatment of moderate to severe psoriasis vulgaris. It binds to CD2 on memory effector T cells and blocks the interaction between LFA-3 on antigen presenting cells (APCs) and CD2 on the activated T cells. It is thought to deplete CD2+T cells by binding to natural killer (NK) cells via its Fc region.² Although its mechanism of action in vivo is incompletely understood, it is thought to improve psoriasis by inducing apoptosis of memory T cells, inhibiting costimulation of T cells, decreasing inflammatory gene expression by multiple cell types and decreasing infiltration of T cells and dendritic cells (DCs) in psoriatic plaques.^{2–4} Over 12 000 patients with psoriasis have been treated with alefacept since its approval in 2003. This paper reviews the available data for the treatment of psoriasis and introduces the results of the recent phase 2 study of alefacept in combination with methotrexate for the treatment of psoriatic arthritis.

CLINICAL TRIALS OF ALEFACEPT IN PSORIASIS

In a randomised, double blind, placebo controlled phase 3 study, patients with moderate to severe psoriasis vulgaris were treated with alefacept 15 mg monotherapy or placebo intramuscularly (IM) on a weekly basis for 12 weeks.⁵ The primary endpoint was predetermined at two weeks following the twelfth injection of alefacept. Patients were then observed for 12 weeks on no therapy except for emollients. At the primary endpoint, 21% of patients achieved at least a 75% improvement in psoriasis disease activity as measured by the Psoriasis Area and Severity Index (PASI75).⁶ However, during the 12 week follow up period, an additional 7% of patients achieved PASI75. A second 12 week course of alefacept resulted in an additional 10% of patients achieving PASI75 with an overall response of 43% of patients reaching PASI75.⁷ Approximately half of the patients reached PASI50 at any time during the first course, and after a second course, 69% reached PASI50.⁷ Unfortunately, the extent of circulating CD4+ T cell depletion did not predict a patient's response during treatment or follow up.³ Alefacept is a remittive treatment, allowing patients time away from therapy.^{8–11} In those patients achieving a PASI75 or better at any time during the first course of therapy, the time until loss of a PASI50 response was a median of 209 days.⁸ Treatment with multiple courses of alefacept showed increasing efficacy and

there was no evidence of tachyphylaxis during multiple courses of treatment¹²

Monitoring drug safety

The safety profile of alefacept is encouraging, with some patients having received up to nine courses of alefacept in phase 2 and 3 clinical trials and their extensions. There was no increase in adverse events in patients treated with alefacept compared with placebo.⁵ Consistent with memory effector T cell depletion as a mechanism of action was the requirement for weekly monitoring of circulating CD4+ T cell counts during the 12 dosing weeks in phase 3 clinical trials. Patients did not start taking alefacept if their CD4+ T cell count was <400; dosing was withheld when the CD4+ T cell count fell below 250. However, patients whose CD4+ T cell counts fell below 250 in clinical trials did not experience an increased incidence of infection.¹¹ There was no increased incidence of malignancies, including cutaneous cancers, in clinical trials comparing alefacept with placebo.^{5 11 13} Although larger numbers of patients are needed, repeated administration of alefacept, with some patients having received up to nine clinical trial courses of alefacept, showed a favourable safety profile, with no increase in malignancies or serious infections over repeat courses.¹⁴

Data from nine multicentre, randomised, phase 2 and 3 clinical studies (and their extensions) were integrated to evaluate the safety and efficacy of alefacept in three special, potentially higher risk, patient populations—elderly, obese, and diabetic patients.¹⁵ Elderly patients were those who were ≥65 years of age at the time of the first alefacept dose (n = 99). Obese patients had a body mass index ≥30 kg/m² (n = 652). Diabetic patients were identified as having a history of diabetes (n = 122). The patients received up to four courses of alefacept. Similar proportions of patients achieved PASI75 in all three subgroups as did the total clinical trial population. There were no differences in safety observed in any of the three subgroups compared with the total clinical trial population. As clinical experience with alefacept accumulates, future analyses involving larger numbers of elderly, obese, and diabetic patients will help to confirm these results.

Alefacept demonstrated clinical improvement in patients with special forms of psoriasis. Two patients with palmoplantar psoriasis were successfully treated with a course of alefacept monotherapy¹⁶ in addition to a patient with palmoplantar pustular psoriasis.¹⁷ In exploratory studies, clinically significant improvement in nail psoriasis, which is often difficult to treat, has been noted.^{18 19}

To evaluate the effect of alefacept on immune function, T cell dependent humoral responses to a neoantigen (φX174) and recall antigen (tetanus toxoid) were assessed.²⁰ Psoriatic patients were randomised to alefacept (7.5 mg intravenously weekly for 12 weeks) or control group. The alefacept group received φX174 immunisations at weeks 6, 12, 20, and 26 and tetanus toxoid at week 21; controls received φX174 at weeks 6 and 12, and tetanus at week 10. Mean anti-φX174 titres were comparable in the two groups. There was no difference in the

percentage of responders (anti- ϕ X174 IgG $\geq 30\%$ of the total anti- ϕ X174) between the alefacept and control groups (86% and 82%, respectively; $p = 0.73$). The percentage of patients whose anti-tetanus toxoid titre increased ≥ 2 times the baseline was also similar (alefacept, 89%; control 91%). Thus, a single 12 week course of alefacept did not impair primary or secondary antibody responses to a neoantigen (despite the fact that immunisation occurred during the trough of CD4+ T cell counts) or memory responses to a recall antigen. Alefacept treatment appears to maintain a humoral immune response to vaccination, and presumably, infection.

In the USA, alefacept is indicated in patients with moderate to severe psoriasis vulgaris who are candidates for systemic or phototherapy. Patients must have circulating CD4 count of at least 400 prior to starting alefacept. Currently, CD4 T cell counts must be monitored weekly and alefacept doses should be held if the CD4 count falls below 250. Patients receive 12, weekly doses of alefacept 15 mg IM followed by a 12 week observation period. If their psoriasis flares during this observation period, patients may be offered a second 12 week course of alefacept. There are patients who have received up to 10 courses of alefacept in clinical trials or in community practice, but the numbers of these patients are still limited.⁷⁻¹¹ Studies are under way to determine if less frequent monitoring of circulating CD4+ T cells—both every two weeks and monthly—is equivalent to the current weekly monitoring requirement. To date, there have been no safety related issues surrounding reduced monitoring or in patients with CD4+ counts that went below 250 during treatment.²¹ In addition, long term efficacy and safety databases have been established for alefacept as it is used by community and academic dermatologists. In the 12 000 patients treated to date, no new safety liabilities have been reported.

COMBINATION THERAPIES

Although the package insert for alefacept cautions against combining with other immunosuppressive drugs, in clinical practice it is necessary to at least overlap alefacept with ultraviolet B (UVB) or traditional systemic agents (methotrexate, ciclosporin, acitretin) due to the delay in the onset of action of alefacept. Studies of small series of patients, tapered off either methotrexate or ciclosporin over a few months while initiating a single 12 week course of alefacept therapy, proved to be successful for most patients.²²⁻²⁶ There was no increase in toxicity of methotrexate, ciclosporin, or alefacept during the time period in which the drugs were overlapped. Narrowband and broadband UVB therapy have been combined with alefacept in single centre studies without an increase in skin cancer or other adverse events. It is difficult to assess if the combination of UVB phototherapy with alefacept is more efficacious than UVB alone as there was no UVB monotherapy cohort in either series of patients.²⁷ There are no reported data on the combination of alefacept with psoralen plus UVA (PUVA).

Demonstration of clinical efficacy in psoriatic arthritis and decreases in synovial T cell and macrophage infiltration were demonstrated in an open study of a small series of psoriatic arthritis patients treated with alefacept 7.5 mg intravenously dosed once weekly for 12 weeks.²⁸ Most recently, a phase 2 study of alefacept in combination with methotrexate for psoriatic arthritis was presented. In this study, psoriatic arthritis patients with three or more tender and swollen joints and who were on stable doses (10–25 mg/week) of methotrexate for at least three months, were randomised to receive either placebo ($n = 62$) or alefacept 15 mg IM ($n = 123$) per week for 12 weeks.²⁹ Responders were defined as those patients achieving at least 20% improvement (American College of Rheumatology (ACR20)) in clinical arthritis activity. The primary endpoint was at week 24, three

months after the last dose of alefacept. At baseline the mean methotrexate dose was approximately 14 mg/week. Baseline weight, duration of psoriatic arthritis, number of tender and swollen joints, pain score, quality of life score (Heath Assessment Questionnaire, disability index (HAQ-DI)), physician and patient global assessment scores, and erythrocyte sedimentation rates were comparable in both cohorts. The baseline C-reactive protein was slightly higher in the placebo (16.7) as compared with the alefacept treated (13.8) cohort. At the primary endpoint (six months), 54% of the alefacept versus only 23% of the placebo cohort achieved an ACR20. There were no increased numbers of adverse events in the alefacept treated cohort compared with the placebo cohort. Alefacept in combination with methotrexate was evaluated in a small pilot study in rheumatoid arthritis, with a significant proportion of patients achieving ACR20 compared with placebo.³⁰

CONCLUDING REMARKS

Unanswered questions remain regarding the mechanism of action of alefacept in psoriasis:

- If depletion of memory T cell via apoptosis is a predominant mechanism of action why is the onset of action of alefacept delayed?²
- Why is it that depletion of circulating CD4+ T cells is not predictive of clinical response?¹¹⁻¹³
- If memory T cells are pathogenic, why do only a third of patients achieve PASI 75?
- If CD4 memory T cells are depleted by alefacept why is the switch from IgM to IgG in primary immune responses to vaccination intact?

Opportunities to increase the utility of alefacept include:

- identifying before initiation of treatment, those psoriasis patients who are likely to have a good clinical response to alefacept
- accumulating more efficacy and safety data on the use of alefacept in combination with UVB and systemic psoriasis therapies since alefacept's onset of action delayed
- evaluating other dosing strategies with alefacept
- extending the use of alefacept to other T cell mediated diseases.

Competing interests: A B Gottlieb is a consultant, speaker, and investigator for Biogen Idec, Inc.

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