Alefacept for psoriasis and psoriatic arthritis

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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.

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. The primary endpoint was predetermed 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 (PASI 75). However, during the 12 week follow up period, an additional 7% of patients achieved PASI 75. A second 12 week course of alefacept resulted in an additional 10% of patients achieving PASI 75 with an overall response of 43% of patients reaching PASI 75. Approximately half of the patients reached PASI 50 at any time during the first course, and after a second course, 69% reached PASI 50. Unfortunately, the extent of circulating CD4+ T cell depletion did not predict a patient’s response during treatment or follow up. Alefacept is a remittive treatment, allowing patients time away from therapy. In those patients achieving a PASI 75 or better at any time during the first course of therapy, the time until loss of a PASI 50 response was a median of 209 days. Treatment with multiple courses of alefacept showed increasing efficacy and there was no evidence of tachyphylaxis during multiple courses of treatment.

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. 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. There was no increased incidence of malignancies, including cutaneous cancers, in clinical trials comparing alefacept with placebo. 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.

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. 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 PASI 75 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, further 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 monotherapy in addition to a patient with palmoplantar pustular psoriasis. In exploratory studies, clinically significant improvement in nail psoriasis, which is often difficult to treat, has been noted. To evaluate the effect of alefacept on immune function, T cell dependent humoral responses to a neosatigen (ϕX174) and recall antigen (tetanus toxoid) were assessed. 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-αXΣI74 IgG ≥30% of the total anti-αXΣI74) 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 after 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 T cell counts 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. 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?

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?
- Why is it that depletion of circulating CD4+ T cells is not predictive of clinical response?
- 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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REFERENCES

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