Alefacept

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Plaque psoriasis is a chronic inflammatory and hyperproliferative skin disease characterized by an increase in memory effector T-cells within psoriatic lesions. An increased understanding of the pathophysiology of psoriasis coupled with biotechnologic advances has led to the development of more specific targeted therapies. These therapies have the potential to provide a specific therapeutic intervention while avoiding potential adverse events associated with traditional systemic agents. Alefacept is a novel biologic agent that selectively reduces memory T-cells whilst leaving naive T-cell populations intact. This article reviews the clinical profile of alefacept in the treatment of psoriasis and other emerging indications. Emphasis is on the results of recently published data designed to clarify the optimal use of this promising new therapeutic option.

Keywords: alefacept, biologic therapy, psoriasis, review, T-lymphocytes

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Psoriasis is a genetic chronic, inflammatory, hyperproliferative skin disease characterized by scaly, red cutaneous plaques commonly presenting in the first three decades of life [1,2]. An increase in $CD4^+$ and $CD8^+$ memory effector T-cells leads to the release of multiple cytokines producing hyperproliferation of keratinocytes. The pathogenic role of T-cells in psoriasis is evidenced by their ability to induce and sustain psoriasis and by the observation that eliminating T-cells is effective in the treatment of the disease [2]. In fact, the serendipitous discovery of the dramatic effect of cyclosporine in a patient with psoriasis in 1979 produced a revolution in our understanding of the immunopathogenesis of psoriasis and the development of more specific therapeutic (biologic) agents [3].

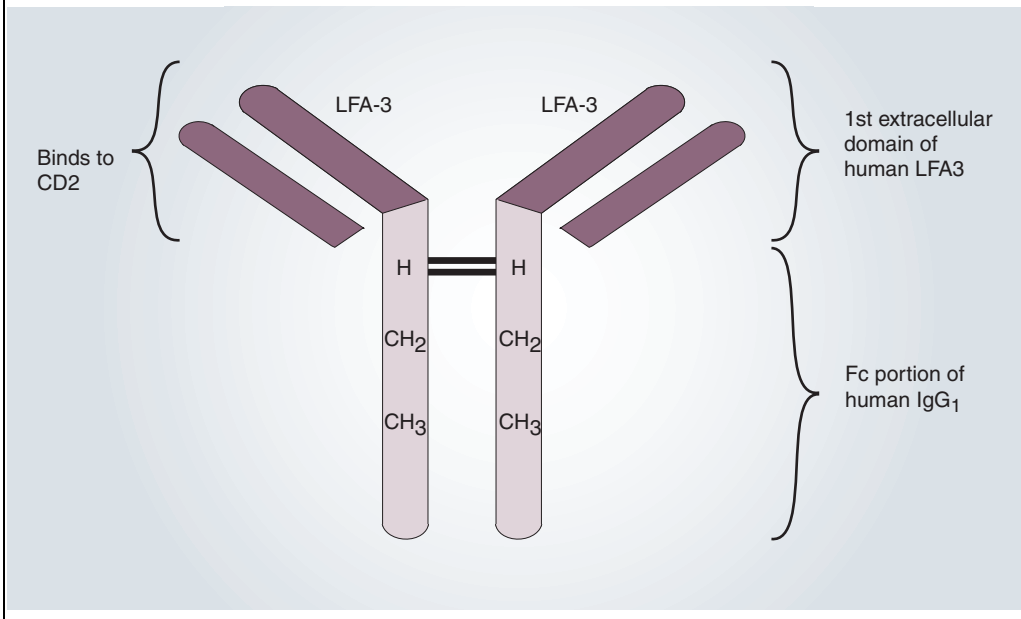
Psoriasis has considerable clinical and psychologic consequences. The National Psoriasis Foundation recently surveyed its members and found that among patients with moderate-to-severe disease, 77% considered it to constitute a moderate-to-large problem [101]. This survey found that of the estimated 4.5 million patients with psoriasis, approximately half a million considered their disease to be a major problem and 1 million were dissatisfied with their therapy [4]. The burden of disease and dissatisfaction with available therapies was highest among those with the greatest degree of disease involvement [4]. These results underscore the fact that conventional systemic therapies for the treatment of psoriasis, while effective in the short term, are suboptimal. In general, traditional therapies do not specifically address the underlying pathologic abnormality [5]. Most of these therapies (with the exception of psoralen plus ultraviolet [UV] A light) are suppressive, with the disease returning to pretreatment (or greater) levels within weeks to a few months after therapy is discontinued [6]. Other disadvantages with traditional therapies include specific organ toxicities such as liver and bone marrow toxicities with methotrexate, renal toxicity and hypertension with cyclosporine, teratogenicity with retinoids, and an increased risk of skin cancer with phototherapy and photochemotherapy [7,8].

The recognition of psoriasis as an immune-mediated disease and the evolution of biologic therapies – protein products that are derived from recombinant DNA techniques to inhibit or imitate naturally occurring proteins in the body – have driven the development of a number of new compounds for the treatment of psoriasis [2]. Alefacept was the pioneer biologic therapy approved for the treatment of moderate-to-severe psoriasis in the USA in January 2003. The US Food and Drug Administration (FDA) have recently granted approval to two other biologic agents for the treatment of psoriasis – etanercept and efalizumab – and multiple other agents are in various stages of development. Importantly, these complex proteins are synthesized in various ways leading to different mechanisms of action and product attributes. This review will summarize the pharmacology and key clinical data leading to the approval of alefacept and then expand on further efficacy and safety data since its introduction to identify the role of these differences.

Mechanism of action

Alefacept is a dimeric human fusion protein that is constructed by fusing the extracellular

Figure 1. The structure of alefacept, a fully human fusion protein.

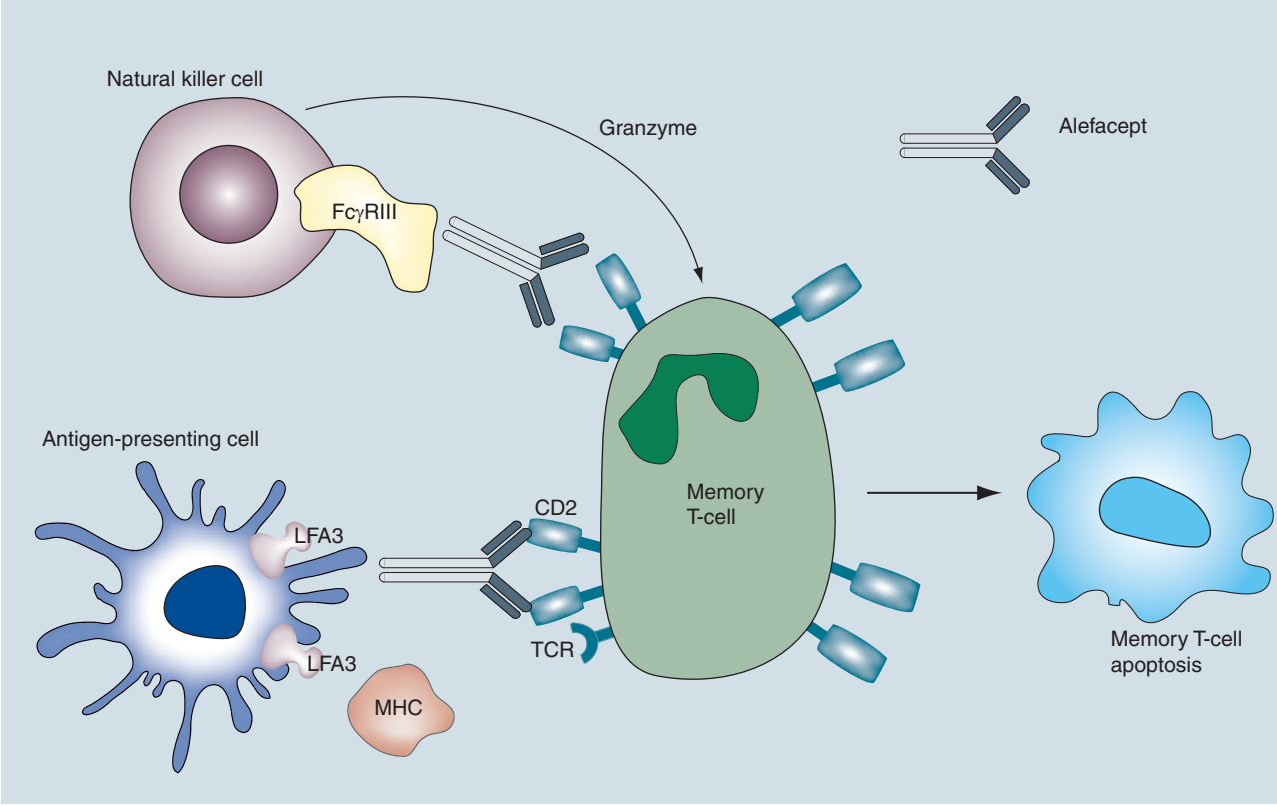


IgG: Immunoglobulin; LFA: Leukocyte function-associated antigen.

CD2-binding portion of the human leukocyte function-associated antigen (LFA)-3 to the CH_2 and CH_3 domains of human immunoglobulin (Ig)G_1 (**Figure 1**) [Amevive® (alefacept) product information. Biogen Inc., MA, USA]. These two components provide alefacept with a dual mechanism of action. The LFA-3 portion of alefacept binds to CD2 on T-cells resulting in the inhibition of T-cell activation and proliferation [9,10]. In addition, the IgG_1 domain of alefacept binds FcγRIII receptors on accessory cells to induce apoptosis of memory T-cells (**Figure 2**) [11]. Since CD2 is upregulated on memory effector T-cells, alefacept has selective effects on this T-cell subtype – the predominant type of infiltrating lymphocytes in psoriatic lesions [12,13]. This action results in a selective reduction in memory T-cells while leaving naive T-cell populations relatively intact. In clinical trials, alefacept consistently produced dose-dependent reductions in circulating total lymphocyte and lymphocyte subset counts, but had no significant effects on naive T-cells, B-cells, or natural killer (NK) cells [14–16]. Mean maximal reductions during intramuscular (im.) dosing of alefacept were 35% for total lymphocytes, 39% for $CD4^+$ T-lymphocytes, and 47% for $CD8^+$ T-lymphocytes. At 12 weeks after the last dose of alefacept, im. recovery was evident – the percentages of patients with normal total lymphocyte, $CD4^+$, and $CD8^+$ counts were 98, 93 and 78%, respectively.

In clinical trials in patients with chronic plaque psoriasis, average reductions in memory T-lymphocytes induced by alefacept have been generally shown to correlate with clinical improvement [14–16]. In the Phase III study of im. alefacept, patients with the most profound and sustained reductions in memory $CD4^+$ T-cell counts had the greatest reduction in disease activity [16]. For example, among patients in the lowest quartile of memory $CD4^+$ T-cell reduction, 21% achieved a greater than or equivalent to 75% reduction in Psoriasis Area and Severity Index (PASI) 75 score during the first course of treatment. The corresponding values for patients in the second, third, and fourth quartiles of memory $CD4^+$ T-cell reduction (increasing cumulative reduction) were 28, 33 and 38%, respectively [16]. A similar trend was observed for changes in memory $CD8^+$ T-cell counts. Further support for the decline in memory T-cell counts as a driver for clinical responses is evident in the observation that maximal mean reductions in these T-cells preceded maximal percentage reductions in baseline PASI [15,16]. Individual results, however, may vary and thus peripheral T-cell counts should not be utilized as a predictive marker of clinical effect. Additional studies have found that the T-cell reductions observed in the peripheral circulation are paralleled by reductions within psoriatic lesions [17,18]. This finding is important as there is active recruitment of memory effector cells into psoriatic lesions during active

Figure 2. Schematic diagram of the dual mechanism of action of alefacept that blocks T-cell activation and induces apoptosis of memory T-cells.



LFA: Leukocyte function-associated antigen; MHC: Major histocompatibility complex.

disease [19]. CD4+ and CD8+ T-cells are capable of secreting a number of pro-inflammatory cytokines, such as interferon (IFN)-γ and tumor necrosis factor (TNF)-α, that are key mediators of keratinocyte proliferation in chronic plaque psoriasis [20]. Lesional skin biopsies from patients with psoriasis have shown reductions in epidermal and dermal memory CD4+ and CD8+ T-cells as well as a reduction in IFN-γ production [18]. In one report, the reduction in memory T-cells in the skin was eightfold greater than the reduction in circulation [17].

Pharmacokinetics

Alefacept was administered either via im. or intravenous (iv.) injection in clinical trials. In healthy volunteers, the relative bioavailability of im. to iv. infusion was approximately 60% [21]. After single 0.04 mg/kg im. or iv. doses, mean maximum plasma concentrations (C_{max}) were higher (0.96 vs. 0.36 µg/ml) and the time to C_{max} (T_{max}) was shorter (2.8 vs. 86 h) with iv. administration compared with im. These findings indicate that higher doses are required with im. administration to achieve equivalent plasma drug concentrations. Thus, the standard im. dose is 15 mg weekly and the iv. is 7.5 mg weekly [Amevive® (alefacept) product information. Biogen Inc., MA, USA]. The elimination half-life of alefacept is approximately 12 days and is consistent with either route of administration [21]. Since its market introduction in 2003, the iv. formulation has been discontinued.

Clinical efficacy & safety

PASI has been adopted as the primary assessment for evaluating the efficacy of new psoriasis treatments. Efficacy assessments in clinical trials of alefacept were performed 2 weeks after the completion of treatment and measured the mean change from baseline. However, many patients do not achieve maximal benefit until well after the last dose (12 weeks) of therapy [14]. Thus, a more meaningful end point may well be the overall response rate, defined as the proportion of patients who achieved a greater than or

equivalent to 75 or 50% reductions in PASI from baseline (PASI 75 or PASI 50, respectively) at any time during treatment or follow-up [22].

Phase II & III trials

The efficacy of alefacept was first demonstrated in a randomized, double-blind, multicenter, dose-ranging Phase II trial in adult patients with chronic (≥1 year) psoriasis that involved over or equivalent to 10% of the patient's body surface area [14]. In total, 229 patients were randomized to receive a single iv. dose of alefacept 0.025, 0.075 or 0.150 mg/kg or placebo once weekly for 12 weeks. The mean decreases in PASI were 38, 53 and 53%, respectively, in the alefacept 0.025, 0.075 and 0.150 mg/kg groups compared with a decrease of 21% for those receiving placebo ($p < 0.001$) [14]. Similarly, the percentages of patients who achieved a PASI 50 were 36, 60 and 56% for the three alefacept groups compared with 27% for the placebo group ($p < 0.001$). Responses were durable after treatment was completed – long-term follow-up revealed that the median time-to-retreatment with alefacept was 10 months among those achieving clearing or near-clearing [23]. Furthermore, there were no reported cases of disease flare or rebound after the cessation of alefacept therapy, a problem not uncommonly observed with traditional therapies [23,24].

The approval of alefacept was based on the results of two Phase III randomized, double-blind, placebo-controlled studies in adult patients with chronic plaque psoriasis [5,25]. One study used iv. dosing of alefacept, while the other used im. dosing [5,25]. In the iv. study, 553 patients were randomized to receive alefacept 7.5 mg or placebo in two 12-week courses of therapy in one of three cohorts (alefacept/alefacept, alefacept/placebo, placebo/alefacept) [5]. In the im. study, 507 patients received a single 12-week course of alefacept (10 or 15 mg) or placebo [25].

After the first course of therapy, alefacept significantly improved clinical outcomes compared with those receiving placebo in both studies (**Table 1**). Reductions in PASI of at least 50% were achieved in 56 to 57% of patients receiving alefacept compared with 24 to 35% of those in the placebo groups [5,25]. The corresponding values for a greater than or equal to 75% reduction in PASI were 28 to 33% and 8 to 13%, respectively. In both trials, a second course of alefacept provided additional benefit (**Figure 3**) [5,15]. PASI 50 and PASI 75 response rates for a second course of iv. alefacept increased to 71 and 40%, respectively, and 69 and 43% for a second course of im. alefacept, respectively [5,15].

The remittent effect of alefacept has been observed in multiple trials, with duration of response defined as the maintenance of PASI 50 response in those who achieved PASI 75 after the first course of therapy. Using this definition, the median duration of off-treatment response was approximately 7 months [5,15]. The duration of response following the second course of therapy was longer, but could not be determined because more than 50% of patients had maintained PASI 50 at the final end point of the study, approximately 1 year after the first dose of study drug [22].

Quality of life assessments were included in the Phase II/III trials and demonstrated that alefacept is associated with significant improvements in health-related QOL as assessed by the Dermatology Life Quality Index (DLQI) and the Dermatology Quality of Life Scales (DQOLS) [26–28]. In the Phase II trial, single iv. treatment courses of alefacept 0.025 to

Table 1. Efficacy of a single 12-week course of iv. or im. alefacept in patients with chronic psoriasis.

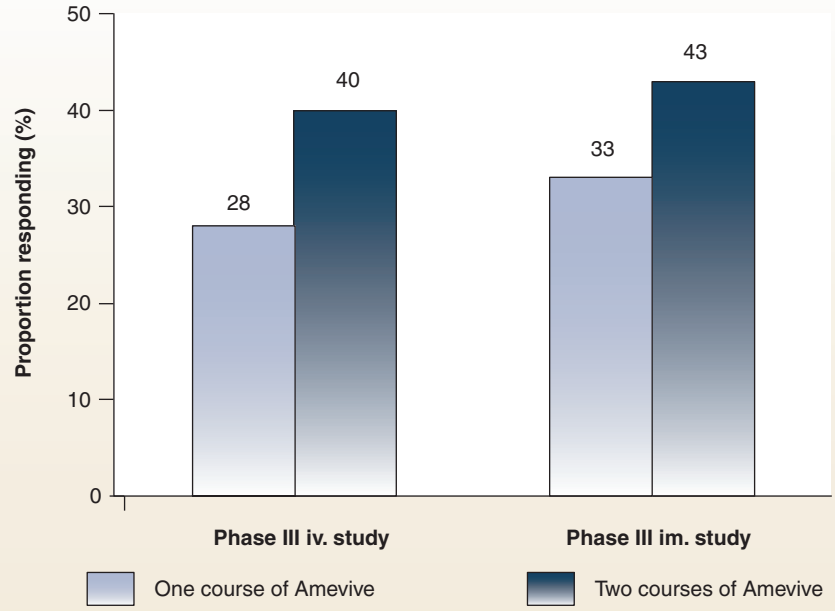
Dose	Efficacy outcome (% of patients)[§]			Ref.
	≥50% reduction in PASI (%)	*≥75% reduction in PASI (%)*	*PGA of 'clear' of 'almost clear' (%)*	
Alefacept 7.5 mg iv. (n = 367)	56[§§]	28[§§]	23[§§]	[5]
Placebo (n = 186)	24	8	6	
Alefacept 15 mg im. (n = 166)	57[§§]	33[§§]	24[§§]	[25]
Placwbo (n = 168)	35	13	8	

im.: Intramuscular; iv.: Intravenous; PASI: Psoriasis Area Severity Index; PGA: Physicians Global Assessment.

[§]Assessed throughout the study period.

[§§]$p < 0.001$

Figure 3. PASI 75 (A) and PASI 50 (B) overall response rates after one and two courses of alefacept show the benefits of a second course of therapy [5,15,25].



PASI: Psoriasis Area Severity index.

0.150 mg/kg once weekly produced statistically significant improvements from baseline in the DLQI overall scale and the DQOLS Symptoms scale [26]. A correlation was found between improvements in clinical efficacy and improvements in health-related QOL. Patients who achieved PASI 50 or PASI 75 had significantly greater improvements in measures of health-related QOL [26]. Similarly, single courses of iv. or im. alefacept in the two Phase III trials produced significant improvements in DLQI and DQOLS [27,28]. For example, patients receiving a 12-week course of im. alefacept 15 mg per week had a mean reduction in DLQI of 4.9 at 2 weeks after the last dose compared with a reduction of 2.7 for those receiving placebo ($p < 0.001$) [27]. The effect was maintained; at 12 weeks after the last dose, the reduction in DLQI was 4.1 for those who received alefacept 15 mg im. and 2.8 for those who received placebo.

Further studies of alefacept

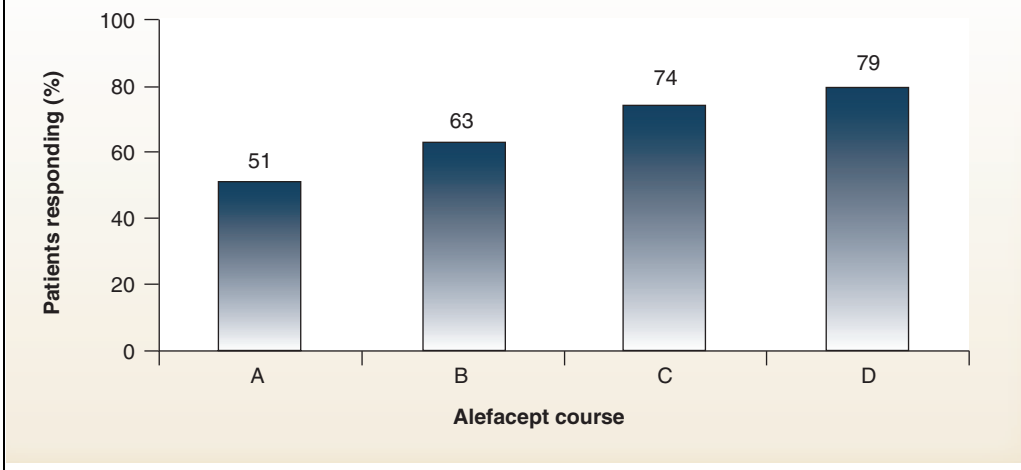
A number of recent studies have assessed clinical issues associated with the use of alefacept. These studies include investigating the additive benefit of multiple courses of therapy, transitioning from conventional antipsoriasis medications to alefacept, combination regimens, alternative dosing schedules, and new therapeutic indications.

Multiple-course therapy

Results of Phase III clinical trials data indicate that patients who respond during the first course of therapy have an 80% likelihood of achieving at least the same, if not greater, response with a second course of therapy [22]. Patients not achieving a PASI 50 during the first course have an approximately 40% chance of this level of response with the second course. Thus, it may be pertinent to consider two or more courses of alefacept in patients responding to the first course of therapy in order to achieve a significant and durable response for patients with this chronic, lifelong disease [29].

As part of the clinical development program of alefacept, patients who completed Phase II and III studies were eligible to participate in open-label extension studies to determine the safety and efficacy of repeated courses of alefacept. The authors recently reported results of these studies evaluating the efficacy of multiple courses [30]. Among the 176 patients enrolled, 126 had received two or more courses, 96 had received three or more courses, and 71 had received four or

Figure 4. PASI 50 response rates in courses A to D at 2 or 12 weeks after alefacept treatment [30].



PASI: Psoriasis Area Severity index.

more courses [30]. There was a progressive increase in the proportion of patients who responded with each successive course of alefacept therapy (**Figure 4**) [30]. The proportion of patients with at least a 50% decrease in PASI was 61% after the initial course of treatment increasing to 79% for those who received four or more courses [30]. There was also no evidence of tachyphylaxis to repeated courses of treatment. Between 75 and 90% of patients who achieved a PASI 50 after a given course of treatment achieved the same level of response with subsequent courses [30]. To date, 362 patients have received four courses of therapy over a 2-year period and 39 patients over seven courses of therapy over a 3-year period, with no evidence of any new safety concerns, especially with respect to infections or malignancies [Biogen Inc., data on file].

Transition from conventional therapies to alefacept

Conventional systemic treatments for psoriasis are associated with safety concerns that limit their long term use. This is a very important aspect of psoriasis treatment because for too long patients have been treated with short, intermittent therapy with inevitable relapses after discontinuation, leading to patient dissatisfaction and a reduction in their quality of life. Two recent studies have assessed strategies for discontinuing conventional antipsoriasis agents (i.e., cyclosporin and methotrexate) and initiating alefacept, especially as the known remission post discontinuation of methotrexate appears to be less than 3 months [31,32]. In the authors' clinical practice, a program for patients receiving methotrexate who are transitioning to alefacept with the aim of maintaining clinical responsiveness and hence quality of life has been developed. Alefacept is initiated at the standard dosage of 15 mg im. once weekly, while the methotrexate weekly dose is slowly tapered down over an 8- to 12-week period, with a goal of discontinuing methotrexate while maintaining clinical response. The authors' examined the effectiveness of this approach in 42 patients as of May 2004 – 40% of patients successfully discontinued methotrexate without flaring and the remaining patients were still being tapered off or were receiving a lower dose of methotrexate [32]. No evidence of increased toxicities were noted; $CD4^+$ T-cell counts during the time patients were receiving both methotrexate and alefacept were comparable to $CD4^+$ counts in patients receiving alefacept alone. Lowering the dose of methotrexate, even in those few in whom it can not be completely discontinued, is a very positive outcome because of cumulative dose methotrexate concerns [33,34]. In addition to our ability to taper the dose of methotrexate, approximately 60% of patients experienced further clinical improvement with the initiation of alefacept [32].

In another ongoing study, a strategy for stopping cyclosporine and initiating alefacept in patients with psoriasis that was well controlled

with cyclosporine was evaluated [31]. The cyclosporine dose is decreased at 4-week intervals over the first 12-week course of alefacept. All seven of the patients completing the initial 12-week phase were able to discontinue cyclosporine while maintaining stable disease control [31]. In addition, adverse events were consistent with those normally seen with alefacept or cyclosporine monotherapy.

Combination regimens

Based on the different mechanisms of action of alefacept and phototherapy with UVB light, an open-label pilot study evaluated the combination of these modalities in 60 patients with chronic plaque psoriasis [35]. All patients received alefacept 15 mg im. once weekly for 12 weeks followed by randomization to one of three groups: no UVB treatment, UVB treatment for 6 weeks, or UVB treatment for 12 weeks. UVB treatment was administered three-times weekly. The combination regimen was well tolerated, $CD4^+$ T-cell counts were similar with all arms of therapy, and there was no evidence that alefacept increased the phototoxicity of the UVB regimen [35]. In terms of efficacy, the combination regimen led to a more rapid onset of response. In addition, a greater proportion of patients in the combination therapy regimens achieved a response at each time point during the 12-week study compared with those receiving alefacept alone as assessed by PASI 50, PASI 75, and Physician Global Assessment (PGA) of 'clear' or 'almost clear'. Additional studies are ongoing to further evaluate the use of alefacept in combination with phototherapy. In clinical practice, the authors' use of narrow band UVB phototherapy for 4 to 6 weeks at the onset of alefacept therapy has produced significant earlier responses [Pers. observation on 200 patients].

Alternative dosing schedules

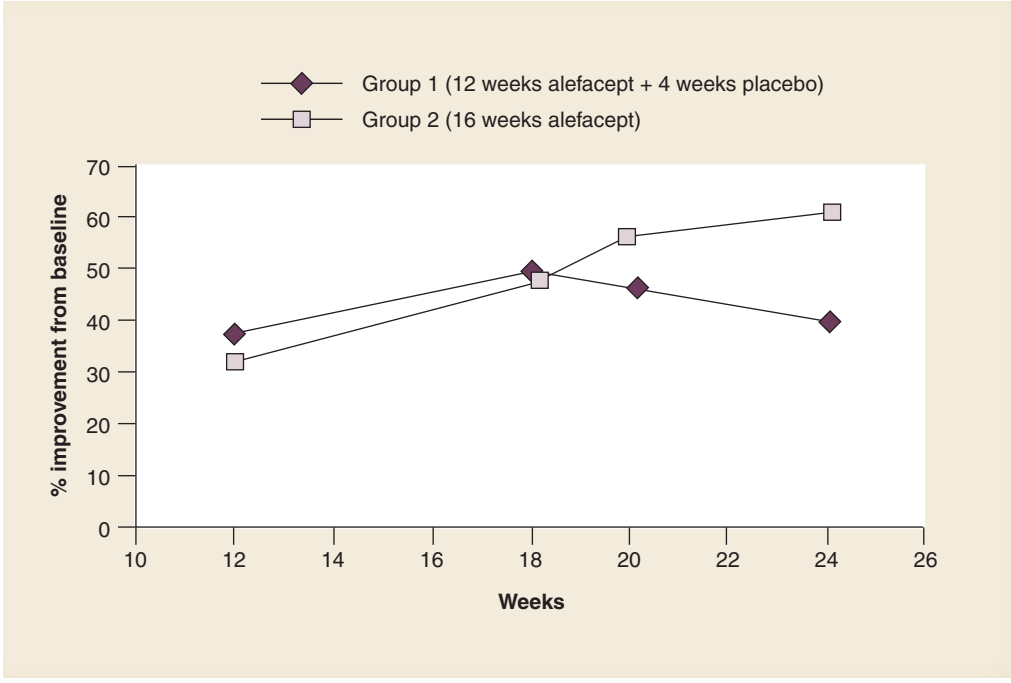
Several alternative dosage regimens are currently under investigation to optimize the use of alefacept. Results of the Phase III trials showed that in patients who achieved a 25 to 74% reduction from baseline PASI the response was truncated by withdrawal of therapy at week 12. Thus, extending the treatment period beyond 12 weeks has been evaluated. The results of a preliminary study comparing the standard 12-week dosage regimen to a 16-week schedule were recently presented [36]. Patients in both groups (n = 10 each) received alefacept 15 mg im. weekly for 12 weeks followed by a double-blind phase where patients received either alefacept 15 mg im. weekly or placebo for an additional 4 weeks [36]. The mean change from baseline PASI decreased throughout the first 18 weeks of the study in both groups. However, after this point, patients in the extended-dose group showed continued improvement in PASI (**Figure 5**). The incidence of adverse events was comparable between treatment groups and similar to prior clinical trials of alefacept. Additional studies are underway with higher weekly doses (up to 30 mg per week) as well as with longer treatment periods (up to 24 weeks).

New therapeutic indications

Preliminary data suggest that alefacept has clinical efficacy in patients with psoriatic or rheumatoid arthritis [37,38]. In a pilot study, 11 patients with psoriatic arthritis and active joint inflammation received alefacept 7.5 mg iv. once weekly for 12 weeks [37]. At the end of 12 weeks of treatment, six patients (55%) achieved a clinical response as assessed by the Disease Activity Score (DAS) [37]. A total of nine patients (82%) fulfilled the DAS response criteria at any point during the study. Significant reductions from baseline in $CD4^+$ lymphocytes, $CD8^+$ lymphocytes, and $CD68^+$ macrophages in the synovial tissue were observed at the end of the treatment period [37]. Clinically, patients achieved reductions in the mean number of tender and swollen joint counts with statistically significant reductions evident as early as week 4 of treatment [37].

A recent randomized double-blind, placebo-controlled trial evaluated the efficacy of alefacept (3.75 or 7.5 mg) or placebo administered iv. for 12 weeks to 36 patients with active rheumatoid arthritis despite treatment with methotrexate [38]. In each of the groups, 67% of patients achieved a 20% or greater improvement as defined by the American College of Rheumatology criteria (ACR) at any time after the first dose [38]. The ACR50 and ACR70 responses were 17 and 8%, respectively, at 6 months in both of the alefacept groups; whereas, no patient receiving placebo achieved an ACR50 or ACR 70 response [38]. Substantial improvements also were observed in the tender and swollen joint counts (**Figures 6 & 7**). The effect was durable; all patients in the 3.75 mg alefacept group who achieved ACR20 at 3 months maintained this benefit at 6 months and an additional 25% of patients achieved ACR20 after cessation of alefacept therapy [38]. In addition, clinical trials are currently underway for alopecia areata, with the potential

Figure 5. Mean percentage improvement in PASI from baseline in patients treated with 12 weeks of alefacept compared with 16 weeks of alefacept [36].



PASI: Psoriasis Area Severity index.

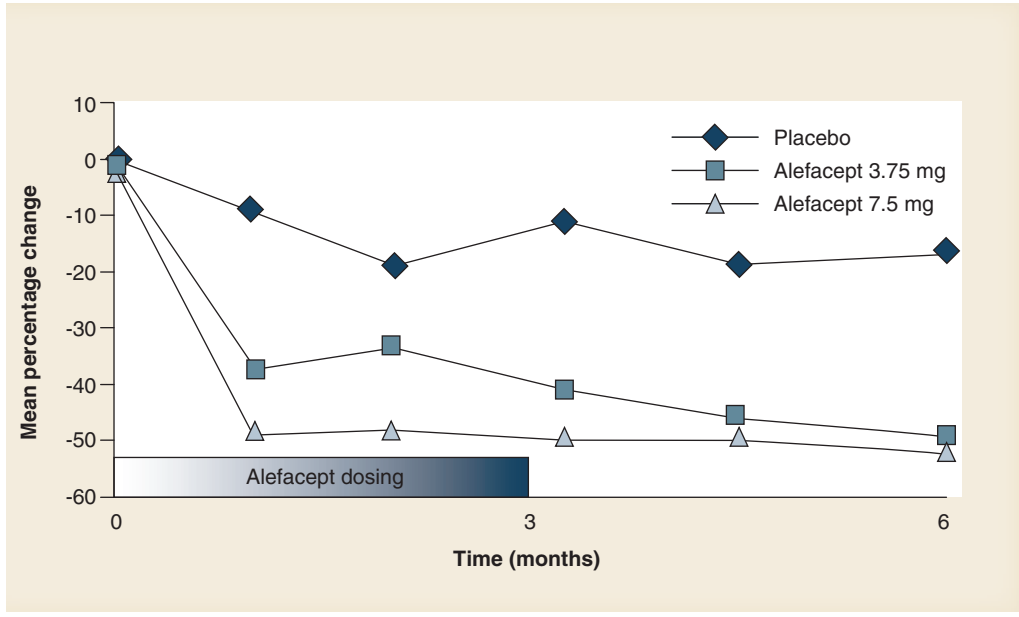
effect on other T-cell-mediated diseases, such as cutaneous T-cell lymphoma, vitiligo, and atopic dermatitis, being explored [Biogen-Idec, Pers. Comm.].

Safety experience

As a result of the effect of alefacept on T-cells, safety assessments of the drug have evaluated not only adverse events and laboratory findings, but also effects on immune responsiveness. After single iv. or im. doses, alefacept was very well tolerated with no significant differences compared with placebo for the most commonly reported adverse events: headache (17 vs. 18%), accidental injury (15 vs. 13%), pharyngitis (15 vs. 13%), and infection (11 vs. 11%) [39]. In addition, the drug produced no clinically significant effects on laboratory values (hematology, blood chemistry or urinalysis), physical examinations or vital signs. In the Phase II/III trials, no association between the dose of alefacept or its effect on T-cells and the incidence of infectious complications was seen [14,25,40]. Overall, there was no evidence from Phase II/III trials of an increased risk of infection or malignancy, and no opportunistic infections were reported [25,40] There is no evidence that the drug produces impairments in the ability of patients' immune systems to mount a primary or secondary response to a new antigen or a memory response to a recall antigen [39–41].

The longer-term safety of alefacept is continually monitored as part of the clinical development program [Biogen Idec, data on file]. The most recent analysis (2004) includes 1869 patients with a mean age of 44.8 years. Of these, 69% are male and 88% are white. The numbers of patients receiving one through to nine courses are 1869, 1152, 554, 362, 171, 56, 39, 21 and 8, respectively. The most commonly observed adverse events (≥5% incidence) in the first course are headache (14%), nasopharyngitis (11%), upper respiratory tract infection (8%), pruritus (8%), arthralgia (6%), fatigue (5%) and nausea (5%). These adverse events are consistently reported in subsequent courses of alefacept with no notable increase in their incidence with multiple courses of treatment. There was no association between the number of courses received and the incidence of adverse events, serious adverse events, or treatment discontinuations due to adverse events. The percentages of patients who have discontinued treatment due to an adverse event or who have had a serious adverse event are consistent over multiple course of therapy – 5% or less. The incidence of antibodies to alefacept remains low

Figure 6. Mean percentage changes from baseline in tender-joint counts over time by treatment group in patients with rheumatoid arthritis.



(≤2% in courses 1–5 and none in courses 6–9) with no effect on efficacy across multiple courses. Additionally, no rebound or tachyphylaxis is observed between treatment courses. Currently, we are evaluating CD4+ T-cell counts in our alefacept-treated patients relating to clinical responsiveness. In our initial 176-patient cohort, no patient, to date, has permanently discontinued therapy due to persistent decrease in CD4+ counts below 250 cells/mm^3, although temporary (1–2 week) disruptions in therapy to allow for counts to rise above 250 cells/mm^3 have been noted.

Alefacept appears to be equally well tolerated in patients who are 60 years of age or older [Biogen Idec, data on file]. In an analysis of the 97 patients who were 60 years of age or over from the Phase III trials, the incidence of adverse events was similar in older patients who received alefacept compared with those who received placebo [Biogen Idec, data on file]. This included the incidence of accidental injury (14–15% vs. 14%), pharyngitis (13–14% vs. 6%), headache (13 vs. 14%), rhinitis (11–12% vs. 8%), and infection (8–10% vs. 3%), respectively, in the alefacept and placebo groups.

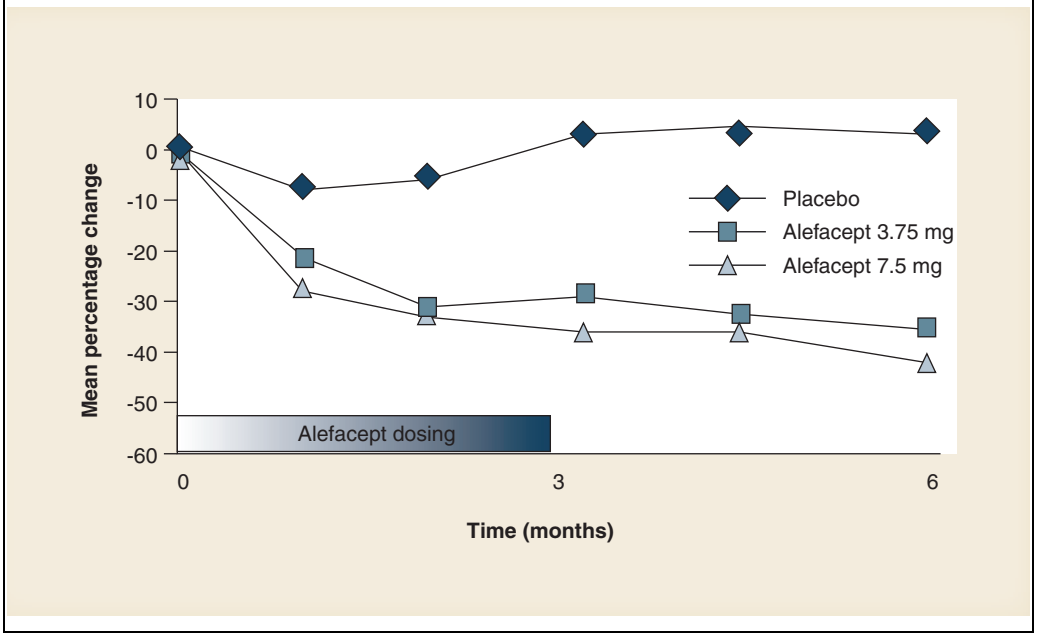
Data regarding the safety of alefacept during pregnancy are limited. Reproductive studies in animals (cynomolgus monkeys), at doses approximately 62-fold greater than those used in humans (on a mg/mg basis), revealed no evidence of impaired fertility or harm to the fetus [Amevive® (alefacept) product information. Biogen Inc., MA, USA]. Based on these findings, alefacept is a pregnancy category B drug. However, since there are no data regarding the safety of alefacept during pregnancy in humans, the drug should be used in pregnant women only if clearly needed [Amevive® (alefacept) product information. Biogen Inc., MA, USA].

Expert opinion

The chronic and relapsing nature of psoriasis is often frustrating for clinicians and their patients. Prior to the development of biologic therapies, systemic therapy was frequently given in an intermittent fashion to provide effective relief of symptoms while balancing the potential short- and long-term toxicities and dosage limitations of individual conventional agents. Physicians used rotational, sequential, and even low-dosage combination schemes to achieve these goals [42]. Accordingly, in a large 17,000 patient survey, only 35% of patients with moderate to severe psoriasis had ever received phototherapy or systemic therapy and 25% were very unsatisfied with the lack of 'aggressive' treatment [43]. The advent of biologic therapies is shifting the treatment of moderate to severe psoriasis to a long-term management approach in a disease that for the majority of patients is lifelong.

Alefacept is a novel and selective biologic agent that is specifically targeted at one of the key pathologic abnormalities of chronic plaque psoriasis-activated memory-effector T-cells that are

Figure 7. Mean percentage changes from baseline in swollen-joint counts over time by treatment group in patients with rheumatoid arthritis.



characteristic of the inflammatory and hyperproliferative activity associated with psoriatic lesions. Results from randomized clinical trials demonstrate that alefacept improves the extent and severity of psoriasis plaques and improves health-related quality of life in a significant proportion of patients. The responses are durable with potential off-treatment remissions of 7 months or more in a subset of patients. In addition, there is no evidence of disease rebound or flare, an effect that may allow patients to spend time off treatment thus reducing the need for continuous therapy in all patients. Furthermore, studies evaluating multiple courses of alefacept therapy demonstrate that the benefit of the drug is cumulative with progressive additive benefit in later courses of therapy and no evidence of tachyphylaxis.

Alefacept has an excellent safety profile with data now accumulated over 3 years of clinical usage, with the spectrum and incidence of adverse events comparable to placebo in clinical trials. Since alefacept inhibits T-cells, there is potential concern that the drug will inhibit normal host defense mechanisms. However, there is no evidence to date that alefacept produces impairments in the ability of patients' immune system to mount a primary or secondary response to a new antigen or a memory response to a recall antigen. This is further supported by findings from clinical trials indicating no increased risk of infection or malignancy compared with placebo-treated patients and no cases of opportunistic infections. Despite these reassuring results, additional clinical experience and longer-term clinical trials are ongoing to confirm that the selective elimination of activated memory T-cells is not associated with potential longer term immune-related adverse effects.

To further establish the role of alefacept in the treatment of plaque psoriasis, a number of other issues are currently under investigation. Initial results suggest that an extended dosing schedule (16-week course) prolongs the clinical response produced by a 12-week course. A 12- and 24-week comparative study course is underway to determine whether even longer treatment durations can further improve clinical outcome. Preliminary data also suggest that alefacept can be safely administered to patients receiving conventional agents (e.g., methotrexate and cyclosporine), allowing patients to transition off (or at a minimum decrease the dose of) these traditional agents with known organ toxicities. In addition, preliminary data suggests that alefacept can be safely combined with UVB phototherapy for potential gains in onset of effect and overall response rate. Nevertheless, additional data from controlled trials are required to establish the effectiveness and role of alefacept when used in these treatment combinations.

Highlights

- Immunopathogenesis of psoriasis and selective reduction of memory effector T-cells.
- Remittive therapy for psoriasis with increasing effectiveness of successive 12-week courses of alefacept.
- Optimal therapeutic index with 16 weeks of alefacept therapy.
- Addition of short-course phototherapy at initiation of alefacept therapy optimizes response.
- Monitoring of CD4 counts is important with optimal requency likely to be reduced to every 2 to 4 weeks during a 12 to 16 week course of therapy.
- Safety data over successive cycles of therapy.
- Transition of patients from traditional systemic therapies (CyA and MTX) with overlapping approach while maintaining optimal safety and efficacy.

What is alefacept's role in the light of the availability of efalizumab and etanercept plus the potential approval in the next 2 years of infliximab and adalimumab? It appears that the two T-cell agents, i.e., alefacept and efalizumab, may be inherently safer for a broader range of psoriasis patients, especially those not candidates for TNF-α agents, for example, history of heart failure, neurologic disease, or tuberculosis. In addition, despite requiring regular CD4 T-cell count evaluations, in our experience of over 200 patients treated not one patient has had to discontinue a full course of 12 injections, suggesting that weekly monitoring of these counts is unnecessary. This is borne out by the recent Canadian approval of alefacept requiring only every other week CD4 evaluations. The slower onset of action is certainly an issue to be discussed with patients, but on balance the potential for long remission in a subgroup of patients, plus what we believe is an excellent safety profile, makes alefacept worthy of consideration in the biologic era of psoriasis therapy. Perhaps its major benefit to us has been our ability to transition patients off methotrexate and cyclosporine who have reached 'the limit' of these two drugs without the inevitable flares previously seen in the majority of patients in the pre-alefacept era [5,15,25].

In summary, alefacept has 'blazed the trail' in the exciting new biologic era for the treatment of patients with moderate to severe psoriasis. As the optimal role of alefacept in the treatment of psoriasis continues to be elucidated, available evidence indicates that this drug provides a significant number of patients with an effective therapeutic option potentially safer than conventional agents while offering renewed hope for achieving disease remission in this distressing, highly visible disease. With the advent of pharmacogenomics, in the years ahead it is hoped that laboratory evaluations will potentially be available to screen patients likely to respond to alefacept, as well as to other biologic agents. Finally, initial data suggests a role for alefacept in the management of psoriatic and rheumatoid arthritis, as well as the potential for treatment of, other autoimmune T-cell-mediated skin disorders in the future.

Outlook

Psoriasis therapy is being revolutionized by the introduction of more target-specific biologic agents. While still in its infancy, this form of therapy is likely to offer more sustained and safer long-term control than our traditional systemic agents which traditionally have been used in shorter courses. Cost restraints are limiting the usage of biologic therapies, underscoring the need for potential pharmacogenetic research in identifying patients likely to respond to the current anti-T-cell agents plus the anti-TNF-α drugs. Psoriasis genetic research has made great strides in the past 5 years, with the next 5 years almost certain to produce improved transgenic mouse models, potential autoantigens, and even more specific therapies. Never before has the outlook for long-term safe control of our psoriasis patients' disease been brighter with groups such as the newly formed International Psoriasis Council and patient advocacy groups, such as the National Psoriasis Foundation, working closely with research and industry to ensure this outcome.

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