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Alefacept: Potential New Therapy for Patients with Moderate-to-Severe Psoriasis

Summary

- ✓ **Alefacept is a new biotechnology product designed for the treatment of patients with chronic plaque-type psoriasis who have disease severe enough to make them eligible for phototherapy or systemic therapy.**
- ✓ **In two randomized controlled phase III trials of patients with moderate-to-severe disease, alefacept showed a modest but statistically significant increase in the number of responders compared to placebo.**
- ✓ **Alefacept's dose-dependent $CD4^+$ T lymphocyte-depleting effect requires monitoring; however, no association has been found between this adverse effect and serious adverse events, particularly infection.**
- ✓ **Due to lack of direct comparative data, it is difficult to predict exactly how alefacept will fit into the current rotational psoriasis therapy paradigm.**

The Technology

In psoriasis, activation of the immune cells, T-lymphocytes, induces changes in the other cells of the skin. T-lymphocytes cause the keratinocytes, the top layer of skin, to become progressively more active, to proliferate more rapidly and to mature abnormally.[1,2] There are also changes that induce blood vessels to grow. As a result, more T-lymphocytes enter the skin layer, the condition gets worse and the patient with psoriasis develops plaques.

Alefacept, a new recombinantly-engineered fully human LFA-3/IgG_1 fusion protein, is designed to treat chronic plaque psoriasis.[1] Alefacept has a dual mechanism of action. The leukocyte-function-associated antigen (LFA) portion prevents the activation and proliferation of T lymphocytes by binding to the CD2 receptors. In addition, the interaction between the IgG_1 portion and the natural killer cells leads to programmed cell death of the memory T-cell subset while leaving the naïve population of T-cells intact.[3,4]

Regulatory Status

On January 31, 2003, the US Food and Drug Administration (FDA) approved alefacept (Amevive®, from Biogen, Inc.) for the treatment of adult patients with moderate-to-severe chronic plaque psoriasis who are candidates for phototherapy or systemic therapy. Biogen Canada Inc. has filed a submission with Health Canada for marketing authorization. As of early February 2003, approval in Canada is still pending (Jocelyn Taguchi, Biogen Canada, Mississauga, ON: personal communication, 2003 Feb 7).

Patient Group

Psoriasis is an inflammatory skin disease characterized by sharply defined, erythematous plaques, covered with distinctive silvery scales.[2,5] There are many subtypes of this disease, but plaque-type psoriasis or *psoriasis vulgaris* is the most common (90%).[2] It affects 1 to 3% of the population worldwide.[2,5] Men and women are affected equally. Although most of the patients with plaque-type psoriasis have mild disease that affects small areas of skin, about 20 to 25% have the moderate-to-severe form.[6] Alefacept has been studied for the treatment of patients with moderate-to-severe psoriasis who are candidates for systemic therapy or phototherapy. These patients are significantly affected by pain, itching and often a reduction in dexterity or mobility due to hand or foot involvement.[5]

Current Practice

At present, there is no cure for psoriasis. Disease management is generally tailored to the severity and location of the disease and is implemented in a step-wise fashion.[2,5] Treatment usually involves topical agents such as corticosteroids, salicylic acid, tars, anthralin, calcipotriol and tazarotene. Systemic agents such as retinoids, methotrexate, cyclosporine or phototherapy with photosensitizers (UVA and psoralen), are primarily reserved for severe disease where more than 20% of the body is affected and where topical agents do not help.[5] Unfortunately, these drugs are associated with serious adverse effects.[2,5] Phototherapy with photosensitizers can cause sunburn (which exacerbates psoriasis), photo-aging and skin cancer. Methotrexate is associated with liver damage, cyclosporin with kidney damage and retinoids with teratogenicity, plus liver and renal dysfunction. Toxicities are dose-related. To minimize the toxicity for patients, a strategy of disease management based on rotating available therapies is used.[5]

The Evidence

The briefing document developed for the FDA review of alefacept reported on two randomized, double-blind, placebo-controlled phase III trials.[7] These trials were performed in patients with moderate-to-severe chronic plaque-type psoriasis, defined as having (a) body surface involvement of 10% or greater, (b) previous treatment with systemic therapy or phototherapy and (c) diagnosis for more than one year.[7] In these studies, the measures of efficacy were the Psoriasis Area and Severity Index (PASI) and Physician's Global Assessment (PGA) scale.

In a published phase III study (protocol C99-711), the safety and efficacy of one and two courses of alefacept [7.5 mg/week intravenously (IV) for 12 weeks] were compared with placebo.[7,8] Subjects were eligible to receive a second 12-week course of alefacept, after a separation of a minimum 12 weeks from the first course, if their disease severity was worse than 'clear' on the PGA scale and their $CD4^+$ T lymphocyte counts were $\geq$250 cells/µL. Patients were randomized using a 1:1:1 ratio to either: (a) two courses of alefacept (n=183), (b) an initial course of alefacept followed by a course of placebo (n=184) or (c) an initial course of placebo followed by a course of alefacept (n=186). Results showed there was a modest increase in the proportion of responders in the patient groups treated with alefacept compared to placebo (Table 1). The patient groups who received alefacept in the second course of study treatment (n=307) showed a greater proportion of responders compared to patients who received placebo (n=142).[7,8] From the group who received alefacept in the first course followed by placebo in the second course, the duration of response to alefacept could be determined. For those who achieved a 75% improvement in PASI, a response of 50% improvement in PASI (a clinically meaningful level of response) was maintained for more than seven months. In terms of safety, alefacept-induced decreases in $CD4^+$ T lymphocyte counts did not recover to baseline, although most returned to the normal range after a prolonged observation period. However, there was no evidence that reductions in lymphocyte counts were associated with serious adverse events, particularly infections.

In the second Phase III study (protocol C99-712), patients with chronic plaque psoriasis were randomized in a 1:1:1 ratio to placebo, to alefacept 10 mg/week or to alefacept 15 mg/week intramuscularly (IM) for 12 weeks.[7] The 15 mg dose produced a modest statistically significant increase in the proportion of responders, as compared to patients on placebo (Table 2). Alefacept showed dose-dependent decreases in $CD4^+$ T lymphocyte counts that persisted in some patients up to the last study visit. Overall, a review of the safety database indicates that treatment with alefacept was well tolerated, although there was a dose-dependent increase in injection site reactions (pain and inflammation) in the alefacept groups compared to the placebo groups.

Administration and Cost

The recommended dose of alefacept is 7.5 mg once weekly IV or 15 mg once weekly IM for 12 weeks. Re-treatment with an additional 12-week course may be initiated provided that $CD4^+$ T lymphocyte counts are within the normal range and a minimum of a 12-week interval has passed since the previous course of treatment. Alefacept induces dose dependent lymphopenia. The manufacturer states that $CD4^+$ T lymphocyte counts of

patients receiving the drug should be monitored weekly for the duration of treatment.[9] In the US, the price of a single course of alefacept will range from US$7,000 - $10,000 depending on the size of the dose.[10] The Canadian price has not yet been established.

Table 1: Major clinical endpoints in the IV study, 7.5 mg weekly

	IV Study Course 1			IV Study Course 2		
	Placebo n=186	Alf 7.5 mg n=367	% RD (95% CI)	Placebo* n=142	Alf** 7.5 mg n=154	% RD (95% CI)
Endpoints two weeks following one course of therapy						
≥ 75% reduction from baseline PASI	4%	14%	10% (6; 15)	7%	23%	16% (8; 24)
≥ 50% reduction from baseline PASI	10%	38%	28% (21; 35)	25%	48%	23% (13; 34)
PGA scale = almost clear or clear	4%	11%	7% (3; 12)	6%	20%	14% (6; 21)
Endpoints any time after the first dose of the course of therapy						
≥ 75% reduction from baseline PASI	8%	28%	20% (14; 27)	19%	37%	18% (8; 28)
≥ 50% reduction in baseline PASI	24%	56%	32% (25; 41)	49%	64%	15% (4; 26)
PGA scale = almost clear or clear	6%	23%	17% (12; 23)	18%	30%	12% (2; 21)

Alf: alefacept; % RD (95% CI): percent risk difference, with 95% confidence interval;
PGA = Physician Global Assessment; PASI = Psoriasis Area Severity Index
* Patients who received alefacept in their first course of therapy
** Patients who received a second course of alefacept

Table 2: Major clinical endpoints in the IM study, 15 mg weekly

		IM Study	
	Placebo n=142	Alf 15 mg n=166	% RD (95% CI)
Endpoints two weeks following one course of therapy			
≥ 75% reduction from baseline PASI	5%	21%	16% (9; 24)
≥ 50% reduction from baseline PASI	18%	42%	24% (14; 34)
PGA scale = almost clear or clear	5%	14%	9% (2; 16)
Endpoints any time after the first dose of the course of therapy			
≥ 75% reduction from baseline PASI	13%	33%	20% (12; 30)
≥ 50% reduction from baseline PASI	35%	57%	22% (12; 33)
PGA scale = almost clear or clear	8%	24%	16% (8; 24)

Alf: alefacept; % RD (95% CI): percent risk difference, with 95% confidence interval

Concurrent Developments

Other biotechnology drugs for the treatment of psoriasis are in various stages of development. The immunomodulators infliximab and etanercept are undergoing clinical testing for psoriasis.[11-13] Another drug in the advanced stages of development is efalizumab, an anti-CD11a (alpha L integrin) recombinant humanized monoclonal antibody.[1,13]

Rate of Technology Diffusion

Alefacept is indicated for the treatment of patients with moderate-to-severe psoriasis, which represent a subset of psoriatic patients. Its place in therapy will depend upon its combined efficacy and safety profile and its cost compared to other agents currently used for treatment of this patient group.

Implementation Issues

Due to the cumulative toxicity of available agents, a strategy of disease management based on rotation of available therapies is used to treat moderate-to-severe psoriasis. Alefacept has the potential to become a component in this rotation. If the US price is representative of the price that will be set for the drug in Canada, cost of therapy will play an important role.

References

1. Granstein RD. New treatments for psoriasis. **N Engl J Med** 2001;345(4):284-7.
2. Ellsworth A. Psoriasis. In: Koda-Kimble MA, Young LY, Kradjan WA, Guglielmo BJ, editors. **Applied therapeutics: the clinical use of drugs.** 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p.38-1-13.
3. Gottlieb AB, Bos JD. Recombinantly engineered human proteins: transforming the treatment of psoriasis. **Clin Immunol** 2002;105(2):105-16.
4. Krueger GG. Selective targeting of T cell subsets: focus on alefacept - a remittive therapy for psoriasis. **Expert Opin Biol Ther** 2002;2(4):431-41.
5. Greaves MW, Weinstein GD. Treatment of psoriasis. **N Engl J Med** 1995;332(9):581-8.
6. **About psoriasis: types & severity.** Portland (OR): National Psoriasis Foundation; 2003. Available: http://www.psoriasis.org/b200.htm (accessed 2003 Feb 11).

7. Marzella L, Papadopoulos E, Wang C. **Briefing document. Biological license application STN BL 125036/0 for alefacept for treatment of chronic plaque psoriasis** [memorandum]. Rockville (MD): Food and Drug Administration; 2002 Apr 29. Available: http://www.fda.gov/ohrms/dockets/ac/02/briefing/3865B1_02_FDA.pdf.
8. Krueger GG, Papp KA, Stough DB, Loven KH, Gulliver WP, Ellis CN, et al. 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(6):821-33.
9. **Amevive® (alefacept)** [product monograph]. Cambridge (MA): Biogen, Inc.; 2003. Available: http://www.fda.gov/cber/label/alefbio013003LB.pdf (accessed 2003 Feb 11).
10. **Amevive approved for treating psoriasis: first of new class of psoriasis therapy** [press release]. Portland (OR): National Psoriasis Foundation; 2003 Jan 31. Available: http://www.psoriasis.org/news/news/2003/20030131_amevive.php (accessed 2003 Feb 11).
11. Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. **Lancet** 2001;357(9271):1842-7.
12. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. **Lancet** 2000;356(9227):385-90.
13. National Horizon Scanning Centre, University of Birmingham. **New treatments for psoriasis** [New and emerging technology briefing]. Birmingham (UK): The Centre; 2002. Available: http://www.publichealth.bham.ac.uk/horizon/PDF_files/Psoriasis.pdf.

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