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The Use of Alefacept in the Treatment of Psoriasis

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ABSTRACT

Alefacept (AMEVIVE™ or LFA3TIP, Biogen) is the newest effective systemic therapy for chronic plaque psoriasis and was approved by the US FDA in January 2003. Clinical studies have shown that alefacept, given via weekly IM or IV injections for 12 weeks, was well tolerated, with no reported serious adverse events. Most significantly, it was found that alefacept provides a long-lasting remittive effect. These findings support the use of alefacept as a viable treatment of psoriasis, without the toxicities associated with some of the current systemic treatments available.

Key Words: alefacept, psoriasis, immunomodulators

Recent evidence clearly demonstrates that psoriasis is mediated by the activation of T-cells, which opens up a new array of therapeutic approaches to improve the clinical and social impact that it has on affected patients. This knowledge gives us the ability to create molecules that selectively target the steps in the activation of T-lymphocytes. Therefore, we will be able to treat psoriasis more specifically, and presumably with fewer side-effects.

Although most psoriasis patients are able to control their condition with topical treatments, there are significant numbers of patients who require phototherapy or systemic treatments. With the exception of PUVA, current phototherapy and systemic immunosuppressive therapies fail to provide long-term remissions. Apart from the inconvenience of frequent phototherapy visits, PUVA is associated with the development of skin cancers, and immunosuppressive therapies are associated with organ toxicities.¹ Biogen, Inc. recently completed studies on the recombinant protein alefacept (a human LFA-3/IgG₁ fusion protein, also known as AMEVIVE™ or LFA3TIP) for the treatment of chronic plaque psoriasis, the most common form of psoriasis.

Mechanism of Action

Alefacept is a selective immunomodulating anti-psoriatic drug that blocks the LFA-3/CD2 interaction necessary for the activation and proliferation of T-cells by binding to CD2 on T-cells. Alefacept also induces selective apoptosis of CD4 memory-effector T-cells by binding to the FcγRIII receptor on natural killer cells and macrophages.^{2,3} CD2 expression is higher on memory-effector (CD45RO+) than naïve (CD45RA+) T-cells. Thus, alefacept has a dual mechanism of action: it selectively binds to and reduces circulating levels of the memory-effector T-cell population. A correlation has been found between that reduction and the improvement of psoriasis.² Since the CD4 count is reduced due to apoptosis, it must be monitored on a regular basis to ensure that it does not drop below 250cells/mm^{3,4}

Clinical Studies

A Phase I study (n=28) showed that alefacept was well-tolerated when administered as either an IM injection, an IV bolus injection (30-second), or an IV infusion (30-minutes); however, pharmacokinetic data support the administration of alefacept via IM or IV bolus injection as opposed to an IV infusion.⁵ A clinical study by Ellis, et al, (n=175) determined the safety and efficacy of repeated courses of 7.5mg alefacept administered by IV bolus. Tolerance was consistent with previous studies and no flares or rebounds were reported after treatment withdrawal.⁶ Lebwohl, et al, in a phase III study, (n=507) found that a dose of 15mg of alefacept given intramuscularly led to significant improvement in the symptoms and severity of plaque psoriasis, suggesting an alternative to IV administration.⁷ Both routes of administration are given once weekly for 12 weeks. These studies demonstrated the potential of alefacept as an effective therapy for chronic plaque psoriasis, for it was well-tolerated and provided a markedly durable clinical response, i.e., patients who responded to a 12-week course of alefacept maintained their improvement for over 7 months post-treatment on average.

Patient Selection and Management

Because this is a systemic therapy to be administered through 12 weekly injections, alefacept will undoubtedly be used in patients with moderate-to-severe psoriasis. The likeliest initial

candidates will be those on cyclosporine, since current guidelines in the United States suggest that cyclosporine therapy be limited to 1 year.⁸ Published results with alefacept show that it is not as effective as cyclosporine, but in contrast to cyclosporine it is not associated with any major organ toxicity such as kidney damage. Moreover, at least with short-term therapy, there does not appear to be an increase in malignancies or opportunistic infections.⁷ Initially, patients treated with methotrexate who are approaching the need for liver biopsies will also be candidates for this therapy, and patients who have received too much PUVA may also be treated with this therapy. Patients treated with ultraviolet B phototherapy may be candidates for alefacept if they prefer the 12-week therapy and the promise of a long remittive effect to frequent phototherapy treatments.

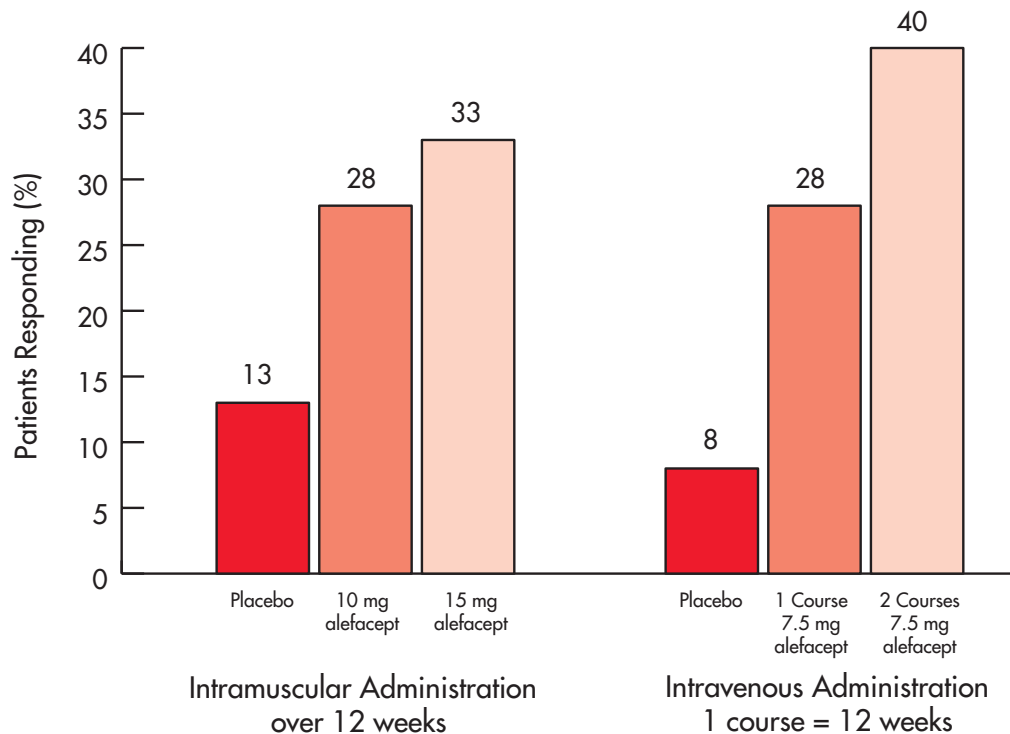
Patient Information

Alefacept should be administered under the supervision of a dermatologist. In clinical trials, alefacept resulted in temporary reduction of T-cells and CD4+ cells. CD45RO+ memory-effector cells, which play a major role in the pathogenesis of psoriasis, were selectively reduced, whereas naïve T-cells were unaffected. Primary and secondary immunizations were not affected by alefacept therapy.

It is possible that regulatory agencies will request regular monitoring of lymphocyte or CD4+ cell counts during the

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Table 1: Patients with $\geq 75\%$ PASI Reduction From Two Phase III Studies



Management of the Ichthyoses

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ABSTRACT

The ichthyoses are a heterogeneous group of inherited scaling skin disorders that can also affect other organs. Management should be directed at both the skin and other sites. Skin therapy is not specific at this time, although new products may offer more directed therapy in the future. Moisturizers and keratolytics are the mainstay of topical therapy. Calcipotriene, retinoids, and for select types, anti-inflammatories such as topical steroids and calcineurin inhibitors have also been used. Systemic therapy is limited to the retinoids. Superinfection of the skin should be anticipated and treated. Pruritus can be disabling. Failure to sweat normally may result in heat intolerance. Eye care should seek to prevent corneal changes resulting from ectropion and more specific changes associated with specific disorders. Hearing can be impaired by the accumulation of material in the external auditory canal. Severely affected children may require caloric supplementation to avoid growth retardation. Affected individuals and their family should be counseled about the long term outlook and the genetic nature of their disorder, and informed of FIRST, the Foundation for Ichthyosis and Related Skin Types, the lay foundation that offers support and information.

Key Words: *ichthyoses*

The ichthyoses are a heterogeneous group of inherited scaling skin diseases (this article excludes acquired ichthyosis, although treatment is much the same with the exception that an underlying cause should be sought). In some cases, other organs are also involved.¹ Although recent studies have revealed that mutations underlie many of the ichthyoses,² specific treatments have yet to follow. Current therapy should be aimed at the skin, other organ involvement, and secondary conditions related to the underlying disorder. Perhaps equally important is to acknowledge the unrelenting nature of the ichthyoses and to direct affected individuals and their families to groups who offer support.

Past and Current Therapies

“The treatment of ichthyosis is essentially external... removal of the scaliness and the maintenance of a soft and pliable condition of the skin.”³ Unfortunately, efficacy of treatment has paralleled neither the understanding of the molecular basis of the disorders nor the expansion of topical treatments seen since this time (Table 1). Moisturizers are the mainstay of therapy of the ichthyoses. They work by increasing the flexibility of the epidermis, hydrating and restoring epidermal barrier function, and by covering and removing scale.⁴ Moisturizers are complex. They have been reviewed recently in this forum.⁵ If one talks with a group of individuals affected with different ichthyoses, it becomes clear that everyone has his/her “best” moisturizer. My interpretation is that these differences reflect not only the way different disorders affect the skin, but also differences between individuals. One approach is to offer general dry skin care along with a list of moisturizers and suggest that affected individuals compare several until the “best” product for that person is identified (see Table 2). Keratolytics and humectants are worth singling out from the moisturizers because

published, double-blind controlled clinical trials of topical therapy demonstrate efficacy.^{6,7} However, the trials are short, the numbers of treated individuals are small, irritation is common, and high plasma urea levels have been reported.^{8,9}

The retinoids and calcipotriene have been used as topical therapy for ichthyosis in a small number of trials.¹⁰⁻¹² Their use has been, for the most part, anecdotal.

Elias and coworkers recently espoused topical therapy based on the underlying defect of specific ichthyoses.¹³ Anecdotal reports support successful use of “a patented ceramide dominant ratio of epidermal lipids [ceramides, fatty acids, and cholesterol]” in some disorders (Elias PM, personal communication, 10.8.2002).

Topical steroids have not been effective in the treatment of the ichthyoses, with the exception of eczema in ichthyosis vulgaris and Netherton syndrome. The inflammation that is present likely results from the underlying barrier defect. Topical tacrolimus is contraindicated in Netherton disease because of the risk of systemic absorption.¹⁴ We have had anecdotal success using topical tacrolimus in Hailey-Hailey and Darier disease, however systemic levels have not been measured.

Systemic therapy with oral retinoids is the most effective therapy available for most of the ichthyoses.¹⁵ It is said that the aromatic retinoids are more effective than 13-cis retinoic acid, but convincing support for this statement is lacking. Although the retinoids have profound effects on epidermal differentiation, the most likely mechanism of action is thinning of the stratum corneum and accelerated loss of scale. The retinoids have significant guaranteed and potential side-effects.¹⁶ Many severely affected individuals use the retinoids chronically, but this should occur only after thoughtful discussion with a physician about the risks and benefits.

Drug	Efficacy	Cost ¹	Side Effects
Topicals			
Moisturizers ⁵	Mild-moderate, variable	Varies widely	Contact dermatitis, can be messy, folliculitis, acne
Keratolytics and Humectants ⁵	Mild-moderate, varies with disorder ^{6,7}	Varies widely	Similar to moisturizers, burning a common complaint
Tretinoin 0.1% cream	Mild, varies with disorder ¹⁰	45g \$83.10USD; generic (Geneva) \$71.47	Irritation, photosensitivity
Tazarotene (Tazorac [®]) 0.05% gel	Mild, varies with disorder ¹¹	100g \$232.01USD	Irritation, photosensitivity
Adapalene (Differin [®]) gel, 0.1% (45 g)	Mild, varies with disorder	45g \$71.69USD	Irritation, photosensitivity
Calcipotriene (Dovonex [®]) 0.005% ointment	Mild, varies with disorder ¹²	100g \$162.13USD	Irritation
TriCeram [®] “a ceramide dominant ratio of epidermal lipids” (www.osmotics.com/triceram.com)	Moderate relief in some ichthyoses (uncontrolled)	\$30USD/100 ml	Cost, ? other
Topical steroids – a large variation in strengths is available	Not efficacious, with the exception of eczema associated with ichthyosis vulgaris and Netherton syndrome	Varies widely	Local atrophy, telangiectasia, striae, superinfection
Tacrolimus (Protopic [®]) 0.1% ointment	Hailey-Hailey, Darier disease (anecdotal experience)	60g tube \$116.25 USD	Irritation, systemic absorption a possible issue (not studied, but documented in Netherton syndrome ¹⁴)
Systemic Drugs			
13-cis retinoic acid (Accutane [®])	Varies with disorder. Makes some disorders (e.g., Netherton syndrome) worse	60mg \$18.22USD /day	Many – mucocutaneous, GI, CNS, lipid, WBC, musculoskeletal ¹⁶
Acetretin (Soriatane [®])	Varies with disorder. Makes some disorders (e.g., Netherton syndrome) worse	35mg \$20.61USD /day	Similar to 13-cis16
Gene Therapy			
Unavailable at this time			

Table 1: Treatment Options - Skin

¹Cost based on average wholesale price, 2001 Drug Topics Redbook

Consideration of the management of the ichthyoses is incomplete without a review of aspects beyond primary skin involvement. Specifics of individual disorders (e.g., the corneal changes in KID syndrome, etc.) are beyond the scope of this discussion. Barrier function in ichthyotic skin is impaired, which often leads to secondary infection. In addition to bacterial infection, viral and fungal (especially dermatophyte) infections are common but can easily be missed in the setting of an underlying blistering or scaling dermatosis if a high index of suspicion is not present.¹⁵ Pruritus can be incapacitating. Sweating is often impaired, perhaps due to eccrine duct occlusion, and precautions

against overheating should be advised. The eye is commonly affected in the setting of ectropion; a corneal ophthalmologist should be involved in care. Ears often plug with cellular debris and require periodic cleaning. Hair and scalp care should address scaling, scarring alopecia, and hair shaft abnormalities leading to fragility. Children with severe erythroderma may display severe growth retardation. This may be the result of increased energy loss caused by evaporative water loss,¹⁷ and may respond to topical treatments and to addressing the nutritional needs of the child. See Table 3. FIRST offers “Fact Sheets” on overheating, retinoids, scalp scaling, ear wax & scale, and itching.

Dry Skin

1. Loss of moisture can be a major cause of dry skin.
2. Factors which may be involved include: low humidity-indoor heat, cold winter air, air conditioning; excessive sun or wind exposure; harsh soaps or detergents; natural aging
3. You do not have to bathe every day. Bathing removes oils from your skin and leads to dry, itchy skin.
4. When you bathe, do not take long baths or showers and do not use extremely hot water.
5. You do not have to use soap on all your skin when you bathe. Use soap only in areas where you feel it is necessary (for example: under your arms, in the anogenital area, etc.)
6. When you use soap, use (bar, not liquid) Dove® soap. Dove® is inexpensive, easy to find, and it is the mildest soap available in this country.
7. Immediately after bathing, blot the excess moisture off and lubricate your skin. You have 5 minutes to lubricate your skin after bathing.
8. Try using only the amount that can be easily rubbed into your skin. It should not take long to rub the lubricant in. There should not be a greasy residue after rubbing in the lubricant.
9. Try purchasing several lubricants and comparing them, one against the other. Use one on one side and one on the other, discarding the less favored after a 2-3 week trial, and add a different product to the comparison until the “best” product for you is identified.

Lubricants (All are available over the counter at your local pharmacy. There are many more than those listed here).

Lotions - first line of treatment

Curel®
Keri® Lotion
Lubriderm®
Moisturel®
Neutrogena Body Emulsion®
Pen-Kera®

Creams – a bit greasier and more effective

Eucerin®

Ointments – still more greasy and effective

Aquaphor®
Vaseline® – the “ultimate” lubricant

Everyone is different. What suits you may not work for someone else. The best lubricant is the one you like the best – you are more likely to use it.

Table 2: Suggestions For Treatment Of Dry Skin

Problem	Approach	Treatment
Secondary skin changes		
• Infection	Maintain a high index of suspicion. Culture, KOH, Tzanck, wet prep where appropriate.	Treat appropriately.
• Pruritus	Exclude secondary infection/ infestation.	Treat erosions and fissures by excluding infection and “sealing” with polysporin ointment. Moisturizers and judicious use of antihistamines may help.
• Decreased sweating	Inquire about perspiration, heat intolerance.	Avoid exposure to excessive heat. Use water “spritzers”, cooling vests.
Eye	Observe for ectropion. Inquire about eyelids that do not close during sleep.	Refer to a corneal ophthalmologist.
Ear	Inquire about fluctuating hearing.	Refer to otolaryngology for ear cleaning and prophylaxis.
Scalp scaling & hair loss	Examine hair, scalp. Inquire about hair loss. Exclude dermatophyte infection.	Overnight humectants and mild keratolytics with occlusion. Gentle shampoo of scalp with soft rubber bristle brush. Use of hair conditioner. Avoid combing hair until it is dry (the force exerted is much greater than that exerted on dry hair due to increased resistance). Treat tinea capitis if present.
Growth retardation	Determine where the child fits on the growth chart and whether s/he is growing.	Refer to dietician for caloric needs. Consider GI evaluation.
The individual and their family	Determine an accurate diagnosis. Ask what questions you can answer.	Refer to an interested “expert” for confirmation of the diagnosis. Inform about FIRST and the National Registry for Ichthyosis and Related Disorders

Table 3: Treatment considerations beyond primary skin involvement.

Conclusion

Time and thought should be given to affected individuals and their families in order to inform them accurately of the diagnosis and prognosis of their disorder. If the diagnosis is in question, referral to a dermatologist with particular interest in these disorders may be helpful. Work with the individual and family to identify the most effective therapy. FIRST, the Foundation for Ichthyosis and Related Skin Types, is a lay foundation that supports affected individuals and their family members (650 N. Cannon Avenue, Lansdale, PA 19446, 800 545-3286, 215 631-1411, 215 631-1413 [FAX], info@scalyskin.org, www.scalyskin.org). The National Registry for Ichthyosis and Related Disorders, 1-800-595-1265, ichreg@u.washington.edu, www.skinregistry.org/, offers one means of "empowerment" and may be able to help with the diagnosis.

Conflict of interest: the author participated in the clinical trial of Lac-Hydrin[®] cream (Westwood).

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12-week course of therapy with alefacept. Patients with a baseline total lymphocyte count below the normal range should not begin treatment with alefacept. Patients should be advised to inform their primary care physician or dermatologist if they develop an infection while undergoing a course of therapy with alefacept.

Alefacept is categorized as US FDA Pregnancy Category B and should be used in pregnant females only if the benefits outweigh the risks. Alefacept has only been studied in patients 16 years and over. Although not approved for pediatric use, this is probably one of the safest systemic treatments for psoriasis. While it is not known if alefacept enters breast milk in nursing females, other antibodies do enter breast milk, so this should be considered in nursing mothers.

Management

Alefacept was approved by the US FDA as an injection for adults with chronic plaque psoriasis. The recommended dose of alefacept is 15mg IM, or 7.5mg IV, once a week over a 12-week period, as supported by results from the Phase III trials.⁷ Patients may be retreated with alefacept on an as needed basis so long as their total lymphocyte and CD4+ T-cell counts are not below the normal range, and at least 12 weeks has passed since their last course of treatment.

While the drug has been studied in an IV and IM formulation, most dermatologists are used to administering IM drugs and may prefer that route of administration. The current developments of biologic therapy have led to infusion centers in some dermatologists' offices, so IV alefacept may be used in these settings. Injection site reactions are avoided by using the IV route and some patients may find this route less painful, but some patients experience chills with the first IV injection, a side-effect that is very uncommon when the drug is administered intramuscularly.

The most commonly observed adverse events that occurred more often with at least a 2% higher incidence in patients treated with alefacept when compared to those treated with placebo were: pharyngitis, dizziness, increased cough, nausea, pruritus, myalgia, chills, injection site pain,

injection site inflammation, and accidental injury. Malignancies and serious infections were observed, but these did not appear to be related to CD4 levels. Most malignancies seen were cutaneous (basal and squamous cell carcinomas) and the rate of malignancy was not greater than what would be expected for the general population.

Conclusion

Alefacept selectively reduces memory-effector (CD45RO+) T-cells, which are involved in the pathogenesis of psoriasis. In clinical studies, alefacept provided significant improvements in patients' psoriasis. Alefacept was well tolerated and, notably, produced long-lasting remissions. There were no reported opportunistic infections and no disease rebounds or flares after drug withdrawal. Alefacept appears to be a useful addition to the psoriasis armamentarium.

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Update on Drugs

Class	Name/Company	Approval Dates and Comments
Monoclonal Antibody	Infliximab <i>Remicade</i> [®] Schering-Plough	The Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMEA) issued a positive opinion in July 2003, for expanded labeling of this monoclonal antibody to include maintenance dosing for sustaining clinical response in patients with fistulizing, active Crohn's disease who have responded to infliximab therapy.
Gaucher's Disease	Miglustat Oral Capsules <i>Zavesca</i> [®] Actelion	The US FDA approved this oral therapy in July 2003, for the treatment of mild-to-moderate type 1 Gaucher's disease in adults for whom enzyme replacement therapy is not a therapeutic option. This product has already been approved in the European Union.
Anti-acne agent	Isotretinoin 10mg/20mg/40mg capsules <i>Claravis</i> [®] Barr Laboratories	The US FDA approved this generic version of Roche's anti-acne product Accutane [®] in April 2003. Bertek Pharmaceuticals' generic version (Amnesteem [®]) was approved in November 2002.
Drug News		
Immuno-modulatory Agent	GlaxoSmithKline has entered into an agreement to co-promote Fujisawa's topical immunomodulator, Protopic [®] (tacrolimus) in the US. This non-steroidal ointment was approved in the US in December 2000, in 0.03% and 0.1% strengths, for the short-term and intermittent long-term treatment of moderate-to-severe eczema in patients who are intolerant to, at risk from, or not responsive to conventional therapies. The 0.03% pediatric formulation has just been recommended for approval in Japan for use in atopic dermatitis. Gel and cream formulations are in Phase II US clinical trials for psoriasis and atopic dermatitis/psoriasis respectively, while Phase II studies for psoriasis with both strengths were recently started in Europe.	
Depigmenting Agent	SkinMedica recently announced the launch of EpiQuin [™] Micro in the US for the treatment of melasma and post-inflammatory hyperpigmentation. The product is a unique formulation of hydroquinone 4% and retinol entrapped in Microsponge technology. The Microsponge technology provides gradual release of the active ingredient into the skin.	
Drug Warning	Details of the combination trial of Amgen's interleukin-1 (IL1) antagonist Kineret [®] (anakinra), and Amgen/Wyeth's tumor necrosis factor (TNF-alpha) blocker Enbrel [®] were recently reported at the EULAR meeting in Lisbon. In the 242 patient trial, adding Kineret [®] to Enbrel [®] did not improve patient response when compared with Enbrel [®] alone, but did pose a greater risk of serious infection. The results have led to recent European label changes warning against their use together.	
Anti-Acne Agent	Bioglan Pharmaceuticals (Quintiles Transnational) has launched a new 75mg tablet dose of its acne product Adoxa [®] (doxycycline) in the US. The product is already available in 50mg and 100mg tablets for the adjunctive treatment of severe acne.	

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