

Alefacept Treatment for Chronic Plaque Psoriasis

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ABSTRACT

Biologic agents were introduced during the past decade as a new class of treatments for chronic psoriasis. These agents provide therapeutic alternatives to traditional topical and systemic therapies. Alefacept, the first such biologic agent, was approved by the US FDA in January 2003 for the treatment of chronic plaque psoriasis. This review will discuss data from clinical trials that have provided new insights into the efficacy, safety, and cost effectiveness of alefacept as a treatment for psoriasis.

Key words: alefacept, Amevive[®], biologics, plaque psoriasis

Psoriasis is a chronic autoimmune, inflammatory disease that affects an estimated 2% of Americans and Europeans.¹ One-third of psoriatic patients have moderate to severe disease and are candidates for phototherapy or systemic treatment.² Biologic agents developed in the past decade provide additional therapeutic alternatives for these patients. Alefacept (Amevive[®]) was the first US FDA sanctioned biologic agent for the treatment of psoriasis, approval was granted in January 2003.³ Alefacept is a human fusion protein of the CD2-binding region of leukocyte function-associated antigen-3 and the CH2 and CH3 domains of immunoglobulin G₁ and acts to inhibit T cell activation and induce apoptosis of memory T cells.³ Since the introduction of alefacept, 5 other biologic agents have been approved for the treatment of moderate to severe psoriasis, including efalizumab (Raptiva[®]), a humanized form of a murine antibody against CD11a (withdrawn in 2009 due to the increase risk of adverse events); the anti-tumor necrosis factor (anti-TNF) agents etanercept (Enbrel[®]), infliximab (Remicade[®]), and adalimumab (Humira[®]); and the IL-12/IL-23 inhibitor ustekinumab (Stelara[™]). Herein, we review what has been learned during the past decade regarding the efficacy, safety, and cost effectiveness of alefacept as a treatment for psoriasis.

Clinical Trials with Alefacept Monotherapy

Alefacept was effective as a monotherapy for chronic plaque psoriasis (CPP) in several clinical studies. Ellis et al. conducted a phase II, multicenter, randomized controlled trial of 229 patients who received 1 of 3 doses of intravenous (IV) alefacept (0.025mg, 0.075mg, or 0.150mg per kilogram of body weight) or placebo control weekly for 12 weeks, with follow-up for 12 weeks after treatment.⁴ Two weeks after therapy, the Psoriasis Area Severity Index (PASI) score was improved by 38% to 53% in the groups receiving alefacept, compared with 21% in the placebo group. Improvement correlated with a reduction in the number of memory-

effector T lymphocytes with alefacept treatment. Clinical improvement was sustained during the 12-week follow-up period, with 28 patients achieving scores of clear or almost clear of psoriasis, compared with 3 patients in the placebo group.⁴ Long-term follow-up of patients achieving a clear or almost clear response demonstrated sustained improvement for a median of 10 months and for up to 18 months before retreatment was required.⁵ Subsequent phase III trials demonstrated improved clinical efficacy and tolerability in patients receiving two 12-week courses of IV alefacept therapy.^{6,7} Intramuscular (IM) alefacept administered as a once weekly injection of 10mg or 15mg for 12 weeks was proven to be similarly safe and effective in improving CPP, and is a convenient alternative to IV therapy.^{8,9}

Cafardi et al. examined alternative dosing regimens for alefacept to determine whether administration of the drug at double the recommended dose or at an increased loading dose improved overall response in patients with CPP.¹⁰ Measures of efficacy included the percentage of patients achieving a 75% reduction in the PASI (PASI 75), the Physician Global Assessment (PGA) scale of disease severity, body surface area (BSA) involvement, and photographic evaluation of a target lesion. Cafardi et al. found that higher doses of alefacept failed to improve clinical response, but were associated with an increased incidence of adverse events (AEs), including mild infection, headache, pruritus, and erythroderma.¹⁰

In an analysis of phase III clinical trials of alefacept, Menter et al. determined the efficacy of multiple courses of alefacept in patients who failed to achieve a $\geq 50\%$ reduction in PASI after a first course of treatment.¹¹ Clinical response was assessed by PGA and PASI at baseline and every 2-4 weeks during follow-up. Of patients who failed to demonstrate a meaningful response to the first course of alefacept, a majority showed an improved clinical response with a second course of therapy. Successive treatment courses resulted in

incremental clinical improvement, with an increase in the percentage of patients achieving PASI 75 from 29% after 1 course to 54% after 5 courses.¹¹ The results of this study are limited by the open-label, uncontrolled design in the third through fifth courses and the number of patients, which decreased over treatment courses. However, the findings suggest that multiple courses of alefacept are well tolerated and result in continued clinical improvement in psoriatic symptoms, at least in patients whose initial response was such that they chose to undertake additional treatment. Recent data by Goffe et al. from 13 clinical trials in patients with CPP receiving up to 9 courses of alefacept therapy over 5 years provide further evidence that long-term therapy with alefacept is safe and well tolerated.¹²

To date, no randomized controlled trials have directly compared the efficacy of alefacept with other biologics approved for treating psoriasis. To attempt to answer this question, Brimhall et al. performed a quantitative meta-analysis of randomized controlled trials of 4 biologic agents: alefacept, efalizumab, etanercept, and infliximab.¹³ Across all trials, efficacy was measured by achievement of PASI 75 after 10-14 weeks of treatment, and the relative risk and number needed to treat was pooled and compared. The study showed that all agents were efficacious for improving psoriasis, though alefacept was the least effective of the agents studied. Pooled relative risk of achieving PASI 75 was 4, 7, 12, and 19 for alefacept, efalizumab, etanercept, and infliximab, respectively, compared with placebo.¹³ The corresponding numbers needed to treat were 8, 4, 3, and 2. The risk of experiencing 1 or more AEs was lowest for alefacept (9%), compared with efalizumab (15%) and infliximab (18%).¹³ The most common AEs were headache, pruritus, chills, pharyngitis, and upper respiratory infections (URIs). According to the study, none of the agents carried an increased risk for serious AEs.

Additional studies have helped to establish alefacept as a safe and well tolerated treatment for psoriasis. Perlmutter et al. conducted a records review of 201 patients treated with IM or IV alefacept once weekly for 12- or 16-week dosing regimens.¹⁴ Fatigue and arthralgias were the most common AEs, reported in 23% and 17% of patients, respectively. URIs were reported in <4% of patients.¹⁴ Despite concerns that alefacept acts as an immunosuppressant, there were no reports of tuberculosis, or disseminated viral or opportunistic infections. Malignancies were reported in 5 of 201 patients and consisted primarily of basal cell and squamous cell carcinomas in individuals with a prior history of exposure to methotrexate (MTX) and ultraviolet phototherapies.¹⁴

Goffe et al. analyzed the incidences of AEs, including infections and malignancies, in patients receiving long-term alefacept therapy.¹² The group reviewed data from 13 clinical trials in patients who received up to 9 courses of alefacept therapy over 5 years. The most common AEs reported by patients were headache, nasopharyngitis, influenza, URIs, and pruritus.¹² No opportunistic infections or infection-

related deaths were reported. The incidence of infection was unrelated to CD4⁺ T lymphocyte count. The rates of discontinuation due to AEs, serious AEs, and infections or malignancies were low and did not increase with repeated treatment courses.

Alefacept as Part of Multi-therapeutic Approaches

The previous studies demonstrated the safety and efficacy of alefacept as a monotherapy for CPP. However, in the clinical setting a multi-therapeutic regimen is often used to optimize treatment efficacy and minimize toxicity. Perlmutter et al. reviewed the records of 201 patients who received IM or IV alefacept once weekly for the standard 12-week or extended 16-week regimens.¹⁴ Patients receiving IM therapy were treated with either the standard 15mg dose or a double loading dose of 30mg. Investigators analyzed several parameters, including BSA involvement; degree of severity; concomitant topical, photo, or systemic therapy; treatment duration; and response to therapy, defined as improvement relative to baseline, which was based on a graded assessment by the treating physician.¹⁴

A majority of patients demonstrated clinical improvement following a single course of alefacept treatment, with 17% of patients achieving an excellent response and 35% achieving either good or better responses.¹⁴ Half of the patients who achieved an excellent response received an alternative therapeutic regimen, including extended treatment duration or increased loading dose. Over 70% of patients received alefacept with a concomitant therapy, including MTX, cyclosporine, systemic retinoids, or ultraviolet A (UVA)/psoralen plus UVA. Forty-one percent of patients who received alefacept monotherapy achieved a good response or better after 1 course of treatment. Good or better responses were achieved by 42% of patients receiving concomitant phototherapy, 36% receiving systemic retinoids, 27% receiving MTX, and 19% receiving cyclosporine.¹⁴ After only 1 course of alefacept added to an existing therapy, many patients were able to successfully discontinue prior systemic therapies without evidence of disease flare. In addition, patients experienced prolonged disease free periods even after treatment completion. Of the 62 patients for whom remission time could be determined, 43 (69%) experienced remissions of ≥ 6 months, 15 (24%) had remissions of ≥ 1 year, and 3 (5%) experienced remissions lasting ≥ 2 years.¹⁴ The average remission time was 7 months and the maximum remission time was 25 months. This study demonstrated the efficacy of long-term alefacept therapy for psoriasis.

A recent study by Krueger et al. examined the safety and efficacy of multiple courses of alefacept in combination with traditional psoriasis therapy for the treatment of CPP.³ Patients received up to 3 courses of 15mg IM alefacept once weekly for 12 weeks, either alone or with 1 concomitant therapy, and then were observed for clinical response over an additional 12 weeks. Concomitant therapies included topical agents, MTX, cyclosporine, systemic retinoids, and ultraviolet B (UVB). Disease severity was assessed using the

PGA scale. More than 75% of patients improved by 1 PGA category, while greater than 44% improved by 2 or more PGA categories across all treatments.³ Greater than 30% achieved a PGA rating of mild or better with the addition of alefacept to the treatment regimen, compared with 3% at baseline, while 16% achieved a rating of clear or almost clear. Although the study was not powered to assess efficacy between treatments, the authors noted that patients receiving alefacept plus UVB treatment showed greater improvement than patients in any of the other concomitant treatment groups. Similar to previous studies, AEs included mild URIs and non-melanoma skin cancers; however, the incidences were low and comparable across all courses and treatment combinations.³ The results suggest that alefacept is well tolerated and efficacious alone and in combination with other psoriasis therapies.

Cost Comparison of Alefacept & Traditional Therapies

An important factor when selecting from among available psoriatic therapies is cost. Mikhael et al. performed a cost comparison analysis of various psoriasis treatments over a 10-year period in Ontario, Canada.¹⁵ They used a hypothetical patient with moderate plaque-type psoriasis exhibiting a PASI 10 score, 20% BSA involvement, and no joint involvement, and calculated the cost to treat this patient with different therapeutic regimens. The results of their analysis depended on the weight of the patient. In a 60kg patient, alefacept, administered in two 12-week courses, was the most costly therapy, followed by infliximab 5mg/kg.¹⁵ In a 90kg patient, infliximab 5mg/kg was the most costly, followed by alefacept as the second most costly treatment option. The least costly treatment was UVB phototherapy.

A recent study by Beyer et al. analyzed the total cost of systemic psoriasis therapies using a cost comparison model based on costs listed in the Consumer Price Index-Urban.¹⁶ The total annual cost for alefacept therapy, administered in two 12-week courses, was \$27,577 US, significantly more costly than MTX therapy, which was \$1197 US. The authors concluded that despite higher monitoring costs for traditional options, the cost of biologics exceeds those of other therapies.¹⁶

Conclusion

Over the past decade, numerous studies have shown the safety, efficacy, and cost effectiveness of alefacept as a therapy for moderate to severe psoriasis. These studies demonstrate that although alefacept is not the most efficacious or cost effective treatment, it seems to be, at least in our opinion, one of the safest treatments, if not the single safest biologic treatment, available. We did not find any reports of opportunistic infections with alefacept, as have been reported with TNF inhibitors. However, far fewer patients have received alefacept compared with those who have received TNF antagonists, thereby limiting the extent to which we know the overall safety profile of alefacept.

Alefacept is slower to act than and is not as effective as TNF inhibitors for most psoriasis patients. However, the efficacy of

alefacept for a particular patient is, as of now, unpredictable. In practice, there is no single right treatment for all, as some patients place more weight on efficacy, others on safety, and others on the convenience of the dosing regimen. For patients who want the safest biologic therapy (and certainly for those who have failed other options), alefacept may be a good choice of treatment, and it may also have a role in multi-therapeutic approaches to treating psoriasis.

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What is Needed for a Sunscreen to Provide Complete Protection

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ABSTRACT

Human skin is increasingly exposed to sunlight. In order to achieve complete protection against the cumulative detrimental effects from sun exposure, topical strategies must shield against the range of solar wavelengths that can damage the skin. Importantly, the harm sustained by the skin is not limited to that caused by the ultraviolet (UV) portion of the light spectrum, but also includes the adverse effects inflicted by near infrared energy. Consequently, in an attempt to provide the necessary broad spectrum coverage, innovative research continues through the exploration of new compounds and novel combinations of chemical and physical UV filters with molecules that are capable of interfering with and/or preventing the deleterious effects of infrared A (IRA) radiation. Existing examples of infrared-protective active agents include mitochondrially targeted antioxidants of synthetic or natural origin.

Key words: infrared, IRA, photoaging, sunscreens, skin protection, UVA, UVB, ultraviolet

Adverse Skin Effects from Solar Radiation

Despite some positive and health promoting effects from sunlight, it is apparent that high acute, chronic low dose, and/or unprotected exposure have several detrimental effects, including premature skin aging and the development and progression of cancer.¹ For many years the focus of research, and therefore for protective strategies, has been centered on the ultraviolet (UV) part of sunlight, i.e., ultraviolet B (UVB) (290-320 nm) and ultraviolet A (UVA) (320-400 nm), because their relatively high photon energy causes macroscopic skin changes that are visible even after a short duration of exposure. However, UV radiation only accounts for approximately 7% of the sun's energy,² which underlines the necessity to consider the detrimental effects from other parts of the sunlight spectrum. Accordingly, we and others identified infrared A (IRA) (760-1440 nm) as a damaging environmental factor to skin through its ability to engender alterations in gene expression of skin cells at multiple points,³ resulting in accelerated skin aging^{4,5} and contributing to the development of cancer.⁶

It is well known that the most effective protection against UV radiation is sun avoidance, e.g., by limiting exposure, or at least direct exposure during peak times, and by wearing appropriate clothing. However, in Western civilizations the level of sun exposure continues to rise, e.g., for recreational reasons and due to increased life expectancy.

Complete Photoprotection Considers All Relevant Parts of the Solar Spectrum

Taking into account recent findings, it is evident that effective photoprotection must provide more than UV coverage, but rather it should protect against IRA as well. It is estimated that about one-third of solar energy is comprised of IRA, which is capable of deep skin penetration.²

Multipronged Approach to Complete Photoprotection

Modern topical photoprotection integrates both primary protective factors (e.g., organic or inorganic light filtering agents) that absorb or reflect UV radiation and secondary factors (e.g., antioxidants, osmolytes, and DNA repair enzymes) that can disrupt the photochemical cascade triggered by UV-penetration, thereby limiting skin damage.

Primary Photoprotection

Primary photoprotection is achieved by using physical and/or chemical UV filtering agents, which have been key active components in commercially available sunscreens for more than 60 years. The most frequently used physical UV filters are the inorganic micropigments, zinc oxide and titanium dioxide.

Most chemical filters absorb UV energy across a relatively narrow or specific wavelength range, converting UV radiation to longer wavelength photons. Due to the limited absorption spectrum of any single ingredient, a combination of sunscreen actives is required to yield both UVA and UVB protection, but the degradation of some UVA filters by sunlight presents formulary challenges. However, in recent years, tremendous progress has been made in developing more photostable UV filters, such as ecamsule (Mexoryl™ SX) and drometrizole trisiloxane (Mexoryl™ XL) and by formulating efficient combinations, such as avobenzone combined with diethylhexyl 2,6-naphthalate and oxybenzone (Helioplex™). Concerning UV filters used in commercially available products, it should be noted that there are differences between approved agents in the European Union when compared with the US, as the US FDA has been more conservative in sanctioning new chemical sunscreens. As for protection against other parts of the light spectrum (other than UV), these chemical compounds do not provide any benefit beyond their UV specificity.

Secondary Photoprotection

Secondary photoprotection involves the use of active agents to interfere with or counteract the inherent photochemical processes that can induce DNA damage in skin cells. Secondary photoprotection may be achieved by an extremely heterogeneous and constantly growing group of molecules that are termed “actives”. Examples of such actives include antioxidants, osmolytes, and DNA repair enzymes^{7,8} (e.g., photolyase and T4 endonuclease V).

Antioxidants that are typically used in sunscreens and other cosmetic products are comprised of vitamins and polyphenols. Prime examples of vitamins formulated in sunscreens are water soluble vitamin C and lipophilic vitamin E. The term “polyphenols” refers to compounds that possess at least 2 adjacent hydroxyl groups on a benzene ring. Natural polyphenols (e.g., flavonoids and procyanidins) are present in numerous foods and have been demonstrated to provide protective properties through topical application.^{9,10} In addition, antioxidants have also been shown to protect against IRA. Accordingly, significant importance resides with molecules that are targeted toward mitochondria, because of their central role in IRA-induced adverse effects.^{3,5,11,12} However, it should be noted that the precise mechanism of action of topically applied actives remain to be elucidated; there is a need to fully understand their effects at both cellular and molecular levels prior to supporting their therapeutic benefits as photoprotective agents.

Osmolytes are small molecules that control and stabilize the cellular environment by regulating hydration and responses to stress conditions. Osmolytes (compatible organic solutes) are not only utilized by cells to control cell volumes, but they have been identified as integral parts of the cellular defence against environmental noxae. The osmolytes taurine¹³ and ectoine¹⁴ have been demonstrated to protect against detrimental UV effects and are amalgamated into several commercially available sunscreens.

Conclusion

Complete topical photoprotection can only be obtained if a sunscreen formula defends against UVB, UVA, and IRA. Whether additional wavelengths contribute to skin damage is currently not known. In order to achieve as near complete broad spectrum protection as is possible, a sunscreen must combine multiple therapeutic approaches that incorporate both essential elements of primary and secondary photoprotection.

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Update on Drugs

Name/Company	Approval Dates/Comments
Collagenase clostridium histolyticum <i>XIAFLEX™</i> Auxilium Pharmaceuticals	The US FDA approved this novel, first-in-class, orphan-designated biologic in February 2010 for the treatment of Dupuytren's contracture in adults with a palpable cord. The injected enzymes dissolve and weaken the contracted collagen cord. This new treatment represents the only nonsurgical option for Dupuytren's disease.
HPV quadrivalent recombinant vaccine <i>Gardasil®</i> Merck & Co.	Health Canada approved an additional indication for this human papillomavirus (HPV) quadrivalent (Types 6, 11, 16, and 18) recombinant vaccine in February 2010 for the prevention of infection caused by HPV types 6, 11, 16, and 18 and genital warts caused by HPV types 6 and 11 in boys and men 9-26 years of age.
Velaglucerase alfa <i>VPRIV™</i> Shire plc	The US FDA approved this hydrolytic lysosomal glucocerebrosidase-specific enzyme in February 2010 for long-term enzyme replacement therapy for pediatric and adult patients with Type 1 Gaucher disease.
Agalsidase alfa <i>REPLAGAL®</i> Shire plc	The US FDA granted Fast Track designation to this human-cell-line-derived enzyme replacement therapy in February 2010 for the long-term treatment of Fabry disease.
Adalimumab <i>Humira®</i> Eisai Co., Ltd.	Japan's Ministry of Health, Labour, and Welfare approved this fully-human monoclonal anti-TNF-alpha antibody in January 2010 for the additional indications of plaque psoriasis and psoriatic arthritis.

Drug News

Health Canada and Hoffmann-La Roche Limited informed healthcare professionals in February 2010 about important new safety information regarding the association between isotretinoin (Accutane™) and cases of severe skin reactions. As of November 6, 2009, based on the manufacturer's global safety database, a total of 66 cases of severe skin reactions have been reported worldwide in both adults and children. Although the majority of these cases involved other confounding factors, an association between isotretinoin and these severe skin reactions cannot be ruled out. Key updated safety information includes:

- There have been very rare post-marketing reports of severe skin reactions (e.g., erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis) linked with the use of isotretinoin. Severe skin reactions include rash, especially if associated with fever and/or malaise or conjunctivitis (red or inflamed eyes, like "pink eye"); blisters on legs, arms or face and/or sores in mouth, throat, nose or eyes; and peeling skin. Severe skin reactions can start with mild non-specific symptoms such as fever, malaise, chills, aching muscles, headache, sore throat, or stinging eyes. It can take up to 3 days for the skin lesions to develop.
- These events may be serious and result in hospitalization, disability, or death.
- Patients should be monitored closely for severe skin reactions and discontinuation of isotretinoin should be considered if warranted.

More information is available at: http://hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/public/_2010/accutane_2_pc-cp-eng.php.