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# *Possibilities of using Alefacept in the treatment of psoriasis*

Almost 2% of the whole population is affected with psoriasis, common skin disorder (1,4). The course of disease is frequently recurrent and impossible to predict (4,11). The cause of psoriasis so far is unknown, although it appears to be an autoimmune disease with a genetic component to its actiology (4). Psoriatic plaques are characterized by infiltration with CD4+ CD45RO+ and CD8+ CD45RO+ memory effector T lymphocytes (5,12). During the past several years, a new generation of therapies for psoriasis has been in development (1,8,13). These biologic therapies target the activity of T lymphocytes and cytokines responsible for the inflammatory nature of this disease (1,13). It was specifically designed to target the underlying cause of psoriasis — an immune system dysfunction (6). Available therapies are often poorly tolerated, unsatisfactory, with many side effects without making efforts to solve the underlying cause of the illness (9). Alefacept (B-9273, Amevive ) is an immunomodulatory recombinant fully human lymphocyte function associated antigen-3/immunoglobulin G1 fusion protein (LFA-3-Ig) CD2 antagonist (2,3) that targets memory-effector T cells by binding CD2 on the T cell surface (10,14). It combine LFA-3 with the Fc portion of human immunoglobulin IgG (13). Its previous name was LFA3TIP (3).

Amevive has the capacity of binding specifically to T lymphocytes showing CD2 (13). CD2 is expressed maximally in T cells that have been activated and express CD45RO, a sign of a memory T-cell phenotype (13). Alefacept modulates the function and selectively induces apoptosis of CD2 (+) human memory-effector T cells *in vivo* (3). Alefacept reduced circulating CD4+ and CD8+ memory-effector T cells, with relatively no change in naive (CD45RA+) T cells or B cells (9). Alefacept also reduced IFN-phi-secreting Tcells in lesional biopsies of psoriatic skin (9). It was shown in experiments with isoforms of alefacept that drug mediates cognate interactions between cells expressing human CD2 and CD16 to activate cells, e.g., increase extracellular signal-regulated kinase phosphorylation, up-regulate cell surface expression of the activation marker CD25, and induce release of granzyme B (3). In the systems which were used, this signaling is shown to require binding to CD2 and CD16 and be mediated through CD16, but not CD2 (3). Trials using human CD2-transgenic mice and isoforms of alefacept confirmed the requirement for Fc gamma R binding for detection of the pharmacological effects of alefacept *in vivo* (3). Thus alefacept acts as an effector molecule, blocking interactions between Fc gamma R (+) cells (e.g., NK cells) and its ligand to induce apoptosis of sensitive CD2 (+) target cells (3). The majority of authors found that Alefacept was well tolerated and nonimmunogenic (1,2,5,6,8,9,10,12-14). Ellis and Krueger (5) also observed that Alefacept had reduced peripheral-blood memory effector T-lymphocyte

(CD45RO+) counts, and the reduction in the number of memory effector T lymphocytes was correlated with the improvement in psoriasis. These reductions all correlated with the observed clinical effect (9). In 2003 the U.S. Food and Drug Administration (FDA) approved alefacept (Amevive) to treat moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy (6 ). To date, alefacept has been studied in moderate-to-severe chronic plaque psoriasis and in a pilot study of psoriatic arthritis (10). In chronic plaque psoriasis, alefacept produced significant and sustained improvements in psoriasis symptoms (1,2,5,6,8,9,10,12-14).

Alefacept was well-tolerated throughout these studies, with a side effect profile similar to placebo (10,11). There was no evidence of generalized immunosuppression or increased risk of infection or malignancy (1,9). Alefacept is an immunosuppressive agent and has the potential to increase the risk of infection and may also increase the risk of malignancies. Adverse events commonly observed in the first course of placebo-controlled clinical trials were pharyngitis, dizziness, increased cough, nausea, pruritus, myalgia, chills, injection site inflammation, and accidental injury (6). Clinical data obtained to date support the use of alefacept as a safe and remittive therapy for psoriasis (8,10). Alefacept did not alter the primary or acquired immune response in psoriatic patients (1,9,10). Known adverse effects are mild, although the FDA advisory committee remains concerned about the potential for infections and malignancies because of reduced lymphocyte counts (12). It is considered as a drug with good efficacy and safety profile (13).

The drug is injected once a week for 12 weeks, and patients receiving alefacept require weekly blood monitoring of CD4+ T-lymphocyte counts (9). Pham et al. (12) in their trials showed alefacept to be safe and effective at once-weekly doses of 7.5 mg intravenous and 15 mg intramuscular for this indication. The duration of response following one 12-week course of intravenous alefacept was shown to be longer than 7 months. Ellis and Krueger (5) conducted a trial in 229 patients with chronic plaque psoriasis. The patients received once a week intravenous alefacept in three different doses from 0.025 to 0.150 mg/kg. The time of treatment was the same - 12 week as the follow-up time; all together 24 weeks. Ellis and Krueger emphasize that in their first trial twelve weeks after treatment they observed that (12.3% of the whole group) 28 patients who had received alefacept alone were clear or almost clear of psoriasis. It was observed that the subjects treated with Amevive who had improvement of their skin condition, gained the long lasting remission during the next 8 months (13). This phenomenon can be possibly connected with the slow repopulation of the skin with native T cells. No increased incidence of infection was observed nor any incidence of cytokine release syndrome during the treatment (13).

Although alefacept showed activity against psoriatic arthritis, further study is needed to observe the more prolonged effects to treatment with this new biological agent (1,12). There was no evidence of disease rebound or worsening of psoriasis following treatment cessation (9).

## REFERENCES

1. Asadullah K. et al.: Novel immunotherapies for psoriasis. Trends Immunology, 23, 47, 2002.
2. Bashir S. J. et al.: Alefacept (Biogen). Curr.Opin.Investig.Drugs, 2, 631, 2001.
3. daSilva A. J. et al.: Alefacept, an immunomodulatory recombinant LFA-3/IgG1 fusion protein, induces CD16 signaling and CD2/CD16-dependent apoptosis of CD2(+) cells. J. Immunol., 168, 4462, 2002.
4. DiSepio D. et al.: New drugs in the treatment of psoriasis. Expert.Opin.Invest. Drugs, 9, 79, 2000.
5. Ellis C. N. et al.: Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. N.Engl. J. Med., 345, 248, 2001.

6. Gary D.: Vogin. Medscape Staff Report, Feb. 5, 2003.
7. Gottlieb A. B. et al.: Recombinantly engineered human proteins: transforming the treatment of psoriasis. Clin. Immunol., 105, 105, 2002 .
8. Griffiths C. E. M.: Immunotherapy for psoriasis: from serendipity to selectivity. Lancet, 359, 279, 2002.
9. Krueger G. G. Selective targeting of T cell subsets: focus on alefacept – a remittive therapy for psoriasis. Expert. Opin. Biol. Ther., 2, 431, 2002 .
10. Krueger G. G. 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., 47, 821, 2002.
11. Kuenzli S. et al.: Dermatology. Med. Hyg., 60, 89, 2002.
12. Pham D. Q. et al.: Alefacept. A T-cell-specific immunosuppressant to treat moderate to severe plaque psoriasis. Formulary, 37, 346, 351, 2002.
13. Singri P. et al.: Biologic Therapy for Psoriasis. The New Theraupetic Frontier. Arch. Dermatol., 138,675, 2002.
14. Weinberg J. M. et al.: Biologic therapy for psoriasis: the T-cell-targeted therapies efalizumab and alefacept. Cutis, 71, 41, 2003.

## SUMMARY

Alefacept belongs to the new generation of drugs applied in the treatment of psoriasis. It is an immunomodulatory recombinant, fully human lymphocyte function associated antigen-3/immunoglobulin G1 fusion protein (LFA-3-Ig) CD2 antagonist that targets memory-effector T cells by binding CD2 on the T cell surface. It blocks the interactions of leukocyte functional antigen (LFA)-3 with CD2 interaction. This drug is used to treat moderate-to-severe chronic plaque psoriasis and there was conducted a pilot study of psoriatic arthritis. It was observed that Alefacept had reduced peripheral-blood memory effector T-lymphocyte (CD45RO+) counts, cells which are responsible for sustaining the disease. Pharyngitis, dizziness, increased cough, nausea, pruritus, myalgia, chills, injection site inflammation, and accidental injury were recorded. So far, in the conducted trials no generalised immunosuppression or increased risk of infection or malignancy were observed. The possibility of increased risk of infections and malignancies must be considered because of reduced lymphocyte counts.

### Możliwości stosowania Alefaceptu w leczeniu łuszczycy

Alefacept (Amevive) należy do leków nowej generacji, stosowanych w leczeniu łuszczycy. Jest to rekombinowane, immunomodulujące, w pełni ludzkie białko, stanowiące fuzję antygenu związanego z czynnością limfocytów (LFA) oraz 3/immunoglobuliny G1 (LFA-3-Ig), które jest antagonistą CD2 i działa na efektorowe limfocyty T pamięci poprzez wiązanie CD2 na powierzchni komórek T. W ten sposób białko to blokuje interakcje funkcjonalnego antygenu leukocytów (LFA –3-CD2). Lek ten jest stosowany w leczeniu przewlekłej plackowatej łuszczycy w postaciach średnio i bardzo zaawansowanych. Przeprowadzono także badania pilotażowe dotyczące jego stosowania w łuszczycowym zapaleniu stawów. Zaobserwowano, że Alefacept redukuje liczbę efektorowych limfocytów T pamięci (CD45RO+) – komórek, które są odpowiedzialne za utrzymywanie stanu chorobowego. Podczas stosowania preparatu odnotowano zapalenie gardła, zawroty głowy, wzmożony kaszel, nudności, świąd, bóle mięśniowe, dreszcze, odczyn zapalny w miejscu wkłucia oraz przypadkowe zranienia. W dotychczasowych badaniach nie obserwowano uogólnionej immunosupresji, jak również podwyższonego ryzyka infekcji lub chorób nowotworowych. Należy uwzględnić większą możliwość infekcji i chorób nowotworowych ze względu na obniżoną liczbę limfocytów.