

Comments

Dermatology

Dermatology 2004;208:297–306
DOI: 10.1159/000077660

Received: January 5, 2004
Accepted: February 21, 2004

T-Cell Modulation for the Treatment of Chronic Plaque Psoriasis with Efalizumab (Raptiva™): Mechanisms of Action

D. Jullien^a J.C. Prinz^b R.G.B. Langley^c I. Caro^d W. Dummer^d A. Joshi^d
R. Dedrick^e P. Natta^f

^aDepartment of Dermatology and INSERM U346, Hôpital Edouard Herriot, Lyon, France; ^bDepartment of Dermatology, Ludwig Maximilian University, Munich, Germany; ^cDivision of Dermatology, Dalhousie University, Halifax, Nova Scotia, Canada; ^dGenentech Inc., South San Francisco, Calif., and ^eXOMA (US) LLC, Berkeley, Calif., USA; ^fSerono International SA, Geneva, Switzerland

Key Words

Efalizumab · Plaque psoriasis · T-cell modulator · Anti-CD11a · Leucocyte function-associated antigen 1 · Intercellular adhesion molecule 1 · Monoclonal antibody · Psoriasis Area and Severity Index

Abstract

Psoriasis is a chronic, incurable, auto-immune disorder with cutaneous manifestations. New evidence on the central role of the immune system in the pathogenesis of psoriasis increasingly provides insight into pathogenic steps that can be modulated to provide disease control. Numerous biological therapies are in various stages of clinical development, with expectation of providing enhanced safety and efficacy over currently available psoriasis therapies. Efalizumab, a recombinant humanized monoclonal IgG1 antibody, is a novel targeted T-cell modulator that inhibits multiple steps in the immune cascade that result in the production and maintenance of psoriatic plaques, including initial T-cell activation and T-cell trafficking into sites of inflammation, including psoriatic skin, with subsequent reactivation in these sites. This article reviews the pharmacodynamic, pharmacokinetic and clinical effects observed during phase I, II and III efalizumab trials in patients with moderate to severe chronic plaque psoriasis.

Copyright © 2004 S. Karger AG, Basel

Introduction

Psoriasis is characterized by keratinocyte hyperproliferation, abnormal keratinocyte differentiation and inflammatory infiltration of the dermis and epidermis with a predominance of activated CD4+ (helper) and CD8+ (cytotoxic) T cells in the dermis and epidermis, respectively, of lesional skin from psoriasis patients [1–3]. Evidence has accumulated to support an involvement of the immune system in keratinocyte dysfunction and the pathogenesis of psoriasis. Immunosuppressive drugs such as cyclosporine [4] and T-cell-selective immunosuppressive agents such as monoclonal CD4 antibodies [5, 6] or the fusion toxin DAB₃₈₉IL-2 (denileukin diftitox) [7] improve the symptoms of psoriasis, and severe combined immunodeficient mouse models have confirmed the involvement of activated T cells in the pathogenesis of psoriasis [8, 9].

This evolution of understanding psoriasis as a consequence of skin-specific T-cell-mediated events initiated the development of targeted interventions aimed at inhibiting T-cell function. This report provides an overview of the role of T-cell interactions in the pathogenesis of psoriasis and describes the evidence for T-cell-specific immune modulation in the mechanism of action of efalizumab, a humanized monoclonal IgG1 antibody for the treatment of patients with moderate to severe chronic plaque psoriasis.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2004 S. Karger AG, Basel
1018–8665/04/2084–0297\$21.00/0

Accessible online at:
www.karger.com/drm

Denis Jullien, MD, PhD
Service de Dermatologie et INSERM U346
Hôpital Edouard Herriot, Place d'Arsonval
FR–69437 Lyon, Cedex 03 (France)
Tel. +33 4 72 11 04 78, Fax +33 4 72 11 03 23, E-Mail denis.jullien@chu-lyon.fr

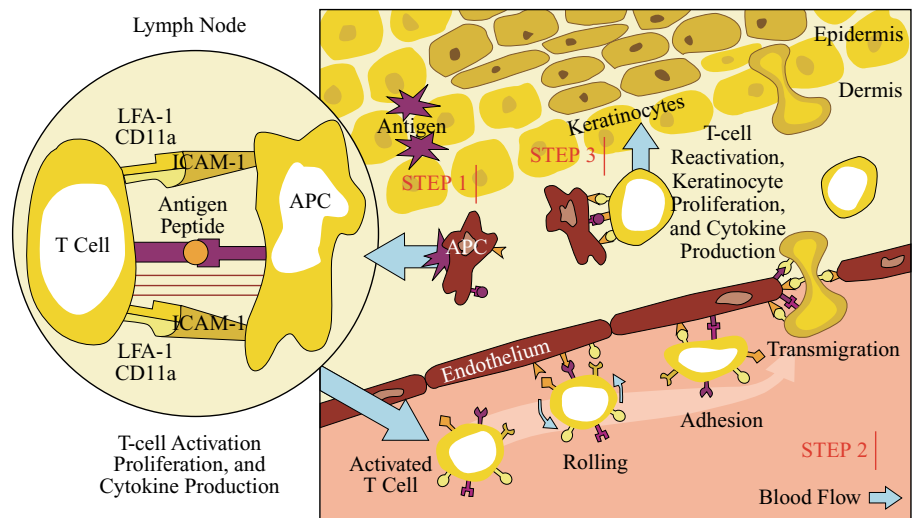


Fig. 1. Key T-cell interactions in the pathogenesis of psoriasis. In order to mediate the cellular changes in the dermis that lead to psoriasis, T cells first undergo 3 key interactions with other cell types. Step 1: APCs must first be activated in the epidermis, where antigen is internalized, enzymatically processed and presented on the APC surface. Activated APCs then travel to the regional lymph nodes, where they interact with naïve T cells, resulting in T-cell activation. Step 2: T-cell binding to venous endothelial cells occurs, followed by

trafficking into dermal and epidermal tissue. Step 3: T-cell reactivation by a second exposure to the specific antigen occurs in the dermis or epidermis. This leads to release of pro-inflammatory cytokines and other inflammatory mediators, which stimulate the increased keratinocyte proliferation. While step 1 occurs only once, it is followed by proliferation of the activated T cells, providing an amplification of the process. Steps 2 and 3 occur in an iterative fashion, causing the persistence of the disease.

T-Cell Interactions in the Pathogenesis of Psoriasis

Current models of psoriasis pathogenesis attempt to incorporate findings from immunological and pathological studies of psoriasis into the classical T-cell activation pathway and typically include 3 key steps: initial presentation of T cells by antigen-presenting cells (APCs), with T-cell activation in primary or secondary immune organs such as the lymph nodes or tonsils¹, and T-cell trafficking to the skin, with T-cell reactivation therein (reviewed in Krueger [10]; fig. 1). It is likely that several types of T cells, including CD4+, CD8+ and natural killer T cells, are important in psoriasis [11, 12]; however, the roles of CD4+ and CD8+ T cells in psoriasis are better understood and are discussed in more detail in this review.

T-Cell Activation

The psoriatic pathway is thought to begin with the antigen-specific activation of naïve T cells. For full T-cell activation to occur, 2 signals are required. According to current assumptions of psoriasis pathogenesis, APCs (classified as Langerhans cells in the epidermis and dermal dendritic cells in the dermis) capture and process an as yet unidentified psoriatic antigen for presentation to T cells via major histocompatibility complexes (MHCs) on the surface of the APC. The nature of this antigen(s) is unknown. Although recent data suggest that lipids may be involved [13, 14], it has been more commonly speculated that endogenous keratinocyte-derived peptide antigens may play a role [15, 16]. Generally, APCs migrate through the lymphatic system to a skin-draining lymph node, where the MHC/antigen complex on the APCs is recognized by specific receptor complexes (TCRs) on naïve (CD45RA+) CD4+ T cells, which have not previously encountered antigen [17]. While there are no data available regarding where psoriatic T cells are initially activated, it is presumed that the process of APC presentation to the TCR occurs in a similar fashion. Naïve T cells enter the lymph nodes via human high endothelial venules,

¹ Prinz JC, Vollmer S: The clonal T cell receptor rearrangements of psoriatic skin lesions are present in the CLA-positive fraction of tonsillar T cells in psoriasis patients with streptococcal sore throat (abstract). *J Eur Acad Dermatol Venereol* 2002;16:113.

with leucocyte function-associated antigen 1 (LFA-1) and intercellular adhesion molecule 1 (ICAM-1) serving as the predominant adhesion molecules. The interaction of the MHC/antigen complex with the TCR is not in itself sufficient for T-cell activation and proliferation. A mandatory second signal also requires the interactions of numerous surface adhesion and costimulatory molecules on the T cell and the APC to form an immunological synapse [18, 19]. Pairs of interacting molecules include LFA-1/ICAM-1 (CD54), CD2/LFA-3 (CD58), CD40 ligand/CD40, and CD28/B7 costimulatory molecules (CD80 and CD86) on the T cell and APC, respectively [10, 18]. Blocking this second signal prevents full T-cell activation.

Secondary Signals in T-Cell Activation

LFA-1, an adhesion molecule expressed by most leucocytes, plays an important role in the initiation of an immune response via formation of the immunological synapse [19, 20]. TCRs sample MHC-peptide complexes expressed on the surface of the APC [21]. Immediately upon detection of the MHC-peptide complex, the TCR activates a T-cell signal transduction cascade [19, 21]. However, the TCR needs a sufficiently long duration of interaction with the APC to allow full activation through the TCR. LFA-1 binds with ICAM-1, expressed on the surface of the APC, forming a tight junction between the TCR and the APC, in what is referred to as the immunological synapse (fig. 2) [21]. The immunological synapse, stabilized by LFA-1/ICAM-1 interaction, allows sustained TCR engagement and signalling, which are required for full T-cell activation and proliferation [19]. Full T-cell activation has been simulated using a lipid bilayer with only MHC and ICAM-1, demonstrating the central role of LFA-1 and ICAM-1 to T-cell activation [19, 21].

T-Cell Trafficking

The activated/memory T cells proliferate, migrate out of the lymph nodes and circulate through the blood stream until their surface receptors recognize areas of cutaneous inflammation, which are marked by high expression of P- and E-selectins, and of the chemokine CCL27 on the endothelial cell surface [17, 22, 23]. The interaction of cutaneous lymphocyte antigen and of the chemokine receptor CCR10 on T cells with P- and E-selectins and with the chemokine CCL27 causes the T cell to roll along the surface of the endothelium, allowing cytokines and/or other inflammatory molecules that are present locally at the site of dermal inflammation to induce the conformational change in markers such as

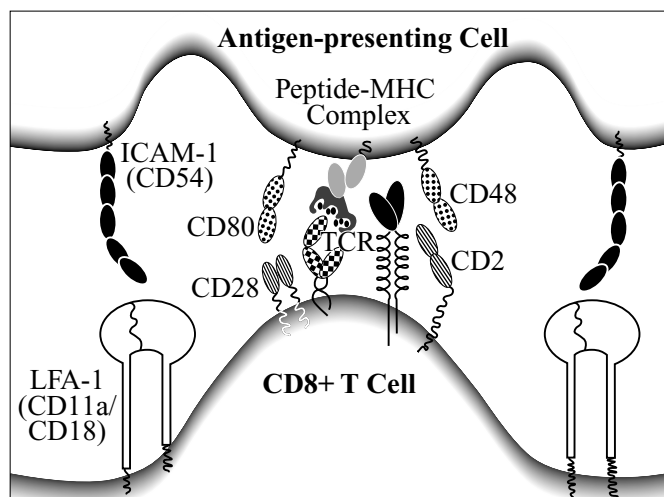


Fig. 2. Formation of the immunological synapse. Reprinted with permission from Elsevier [van der Merwe PA, Barclay AN: Trends Biochem Sci 1994;19:354–358], adapted by Malissen [21].

LFA-1 on the surface of the T cell. Interactions of LFA-1 with ICAM-1, ICAM-2 and ICAM-3, which are up-regulated on activated endothelium, mediate the tight adhesion of the T cells to epithelial cells and facilitate the subsequent flattening and trafficking of the activated CD4+ T cells from the circulation into the dermis (reviewed in Bradley and Watson [24]). Following extravasation, the T cell responds to chemotactic signals from inflammatory cells at the site of inflammation.

T-Cell Reactivation

Once in the skin, the CD4+ T cells interact via the TCR and MHC molecules with APCs (T-cell reactivation), become reactivated in an antigen-specific manner [25, 26] and produce a Th1-like cytokine pattern that includes IFN- γ and TNF- α but not IL-4 [27]. These cytokines are considered to be important mediators of the inflammatory and hyperproliferative changes of psoriatic skin lesions. Furthermore, the activated CD4+ T cells may assist in the activation of CD8+ T cells [28]. CD8+ T cells are cytotoxic T lymphocytes that can kill target cells. As with CD4+ T-cell activation, activation of CD8+ T cells requires secondary costimulatory interactions in addition to interactions between TCR on the T cell and MHC on the APC. The specific APCs for CD8+ T cells are unknown but could be keratinocytes or dendritic cells, or both [15]. CD4+ Th1 cells express CD40 ligand, which interacts with CD40 on APCs, resulting in an increased production of cytokines [28, 29] and up-regulation of co-

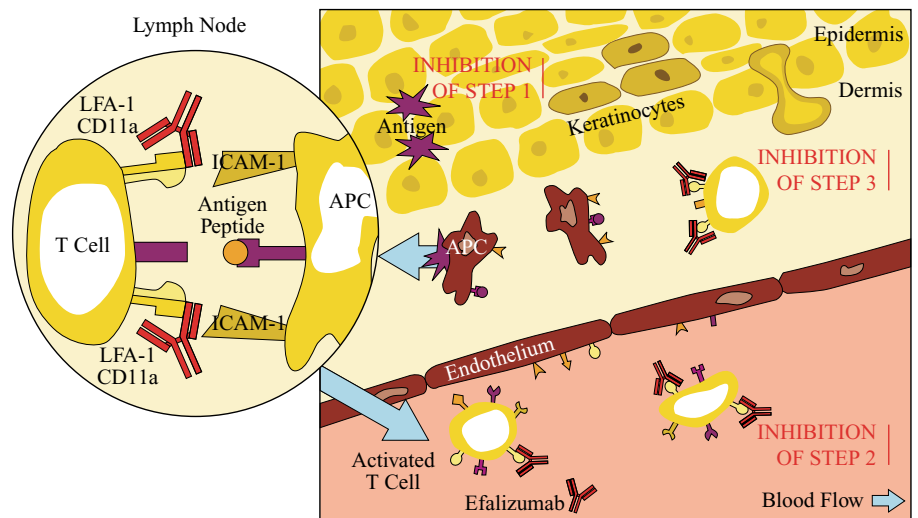


Fig. 3. Efalizumab mechanisms of action. Efalizumab inhibits adhesion of T cells to other cell types by inhibiting the binding of LFA-1 to ICAM-1. This mechanism of action has a number of effects, depending on the cell type, including inhibition of T-cell activation, inhibition of T-cell trafficking and extravasation, and inhibition of T-cell interactions with tissue-specific cells.

stimulatory molecules necessary for CD8+ T-cell activation [28, 30]. In particular, ICAM-1 synthesis is induced by IFN- γ and TNF- α on epidermal keratinocytes [31], which do not normally synthesize this ligand [32]. In addition to LFA-1/ICAM-1, several different costimulatory ligand-receptor pairs may be involved in CD8+ T-cell activation, including CD2/LFA-3 and very late antigen 4/vascular cell adhesion molecule 1 on the T cell and APC, respectively [12]. Activated CD8+ T cells exhibit a type 1 cytotoxic phenotype in psoriasis [1, 33] and release IL-2, IFN- γ and TNF- α . The exact mechanisms by which activated T cells exert their effects to cause the psoriatic phenotype are unknown but could involve interactions of a specific array of cytokines and/or growth factors released by the T cells with the epidermal keratinocytes. Cytokines produced by T-cell clones established from psoriatic skin lesions in vitro may selectively enhance keratinocyte proliferation, which is a hallmark of psoriatic skin lesions [34, 35]. Direct interactions of T cells with epidermal keratinocytes may also be important in driving T-cell activation, in turn contributing to the psoriatic phenotype [15]. Additionally, it is hypothesized that while migrating into the epidermis, CD8+ T cells could induce keratinocyte injury, which in turn triggers keratinocyte hyperplasia as part of an injury response similar to the wound repair response [10].

Blockade of T-Cell Costimulation as a Therapeutic Approach

Because of the important role of LFA-1/ICAM interactions in mediating multiple T-cell processes, targeting

these interactions represents a rational approach to inhibiting the psoriasis disease process. Monoclonal antibodies directed against LFA-1 or its ligands have been found to inhibit T-cell activation in vitro [36], inhibit T-cell-dependent T-cell responses [37, 38], inhibit lymphocyte proliferation responses [39, 40], reduce lymphocyte trafficking and homing [41, 42] and reduce adhesion of T cells to endothelial cells in vitro [43]. One strategy to inhibit LFA-1/ICAM interactions has been to develop antibodies against CD11a, the α -subunit of LFA-1.

Efalizumab: A T-Cell Modulator for the Treatment of Psoriasis

Efalizumab is a humanized monoclonal IgG1 antibody that binds with high specificity and affinity to CD11a (the α -subunit of LFA-1) [44]. According to the mechanisms of T-cell activation explained above, efalizumab targets psoriasis pathogenesis at multiple levels, inhibiting initial T-cell activation in the lymph nodes, preventing binding of T cells to endothelial cells, blocking trafficking of T cells from the circulation into psoriatic skin and preventing reactivation of T cells in the dermal and epidermal layers (fig. 3). By inhibiting these processes, efalizumab may ultimately prevent keratinocyte proliferation and abnormal keratinocyte differentiation from occurring, thus blocking the development of the hallmark characteristics of psoriasis. Data from the phase I/II trials consistently demonstrated that efalizumab provides rapid, specific and reversible inhibition of CD11a on T lymphocytes

[45–48]. Efalizumab has undergone extensive clinical testing, in more than 13 clinical trials involving more than 2,700 patients with moderate to severe chronic plaque psoriasis treated to date.

Efalizumab Pharmacokinetics, Pharmacodynamics and Histological Improvement

Intravenous Administration

Three phase I and II studies investigated the pharmacodynamic properties of efalizumab, either as a single intravenous dose of 0.03–10 mg/kg [45, 49] or repeated weekly administration of 0.1–1 mg/kg/week for up to 8 weeks [46, 48]. Blood samples from treated patients were subjected to fluorescence-activated cell sorter analyses in order to assess the binding of efalizumab to lymphocytes and to assess expression of CD11a on lymphocytes. In the single-dose study, treatment with efalizumab caused a rapid reduction (in less than 24 h) in the level of CD11a expression on T cells, to approximately 25% of pretreatment levels. Circulating concentrations of efalizumab increased with dose. CD11a levels on lymphocytes remained suppressed as long as efalizumab was present in the circulation. Following clearance of efalizumab from the circulation, CD11a expression returned to normal within 7–10 days thereafter. No depletion of circulating lymphocytes was observed. The relationship between circulating levels of efalizumab and CD11a expression on peripheral blood T cells was described via a CD11a-receptor-mediated clearance model [49]. Doses above 0.3 mg/kg were required for the full pharmacodynamic effect. A small increase in total white blood cell (WBC) count occurred approximately 8 h after efalizumab administration, and circulating lymphocyte counts were increased by day 7. Following multiple weekly doses, circulating lymphocytes remained elevated but did not increase further during continuous dosing with efalizumab and returned to baseline following clearance of efalizumab. No long-term treatment effects were observed on the proportion of T cells, B cells and natural killer (NK) cells or on the ratio of CD4+ and CD8+ T-cell subtypes. Furthermore, T-cell CD11a rapidly recovered following plasma clearance of efalizumab. All patients retained humoral immunity.

Histological analysis of psoriasis lesions from patients in the 3 studies showed consistent reductions in epidermal thickness following efalizumab administration [45, 46, 48]. In patients who received repeated weekly doses of 0.3 mg/kg i.v. efalizumab, the number of T cells in the dermis and epidermis was reduced by greater than 50% on day 28 [46, 48]. Furthermore, on day 28 the vast majority of patients demonstrated no detectable CD11a

binding sites in lesional skin [46]. In all 3 studies, efalizumab administration resulted in a reduction in keratin 16 expression in lesional skin. Regenerative epidermal differentiation is marked by synthesis of keratin 16 in supra-basal keratinocytes, whereas in homeostatic differentiation (normal skin) it is not synthesized. The reduction in keratin 16 is therefore indicative of disease resolution. Keratinocyte ICAM-1 levels were also reduced following efalizumab exposure, providing an indirect indication of reduced cytokine production by T cells in the skin. At a dose of 0.6 mg/kg i.v. weekly, efalizumab produced plasma concentrations of approximately 5 µg/ml and maintained down-modulation as well as complete saturation of CD11a binding sites on circulating and plaque T cells. Together, the clinical, histological and pharmacodynamic data from these studies demonstrated that by reducing the available CD11a on circulating and cutaneous T cells, efalizumab can halt the inflammatory process and pathological hyperplasia that are the hallmarks of psoriasis.

Subcutaneous Administration

Three phase I open-label studies investigated pharmacodynamic parameters following subcutaneous administration of efalizumab. In the first study, patients received either a single dose (0.3 mg/kg) or 8 weekly escalating doses (0.5–2 mg/kg) of efalizumab (study HUPS254). In the second study, patients received 12 weekly escalating doses (1–4 mg/kg) of efalizumab (study HUPS256). In the third study, patients received 12 weekly doses of efalizumab (1 or 2 mg/kg/week; study ACD2124g)². Excepting a dose difference between the intravenous and subcutaneous routes, in general the effects of subcutaneously administered efalizumab on circulating lymphocytes in these studies were similar to those previously observed with intravenous dosing. Doses of 1 mg/kg/week or above produced efalizumab plasma concentrations above 5 µg/ml and produced a maximal pharmacodynamic effect. Doses equal to or greater than 1 mg/kg/week were efficacious with no additional benefit from the 2- and 4-mg/kg/week doses. Data from these studies demonstrated that there was a decrease in epidermal and dermal T-cell infiltrates in biopsies, and a clear trend for improvement over

² Mortensen DL, Walicke PA, Kuebler P, et al: The pharmacokinetics and pharmacodynamics of efalizumab following 12 weeks of subcutaneous treatment in patients with moderate to severe plaque psoriasis in a phase I, open-label, multi-center study. *Int Invest Dermatol Meet*, Miami Beach, 2003, poster 379.

the duration of the studies³ [XOMA (US) LLC and Genentech Inc., data on file].

Following efalizumab treatment of 1 mg/kg/week for 12 weeks⁴, there was a reduction in CD11a expression on circulating T lymphocytes to approximately 15–30% of baseline within 1–3 days of administration, and CD11a binding sites were generally more than 95% saturated. Additionally, CD11a expression was down-modulated, and CD11a binding sites were saturated on B lymphocytes, NK cells, monocytes and neutrophils, but to a lesser extent than that observed on T cells. Absolute counts of circulating lymphocytes more than doubled, while levels of monocytes and neutrophils remained stable. Consistent with the increase in lymphocytes, there was an increase in WBC count, which gradually resolved following clearance of efalizumab from the circulation. The increase in peripheral lymphocyte count is presumably due to the inhibition of binding between LFA-1 on lymphocytes and ICAM-1 on endothelial cells, thereby blocking trafficking of lymphocytes into the skin and into other organs. Peripheral blood lymphocyte counts, CD11a expression and available CD11a binding sites returned to pretreatment levels approximately 6 weeks following the final dose of efalizumab, indicating that the pharmacodynamic effects of efalizumab are reversible.

A mechanism of action substudy following treatment with 2 mg/kg/week efalizumab (study ACD2142g)⁵ demonstrated that efalizumab markedly reduced anti-CD3-mediated T-cell activation and that this effect was reversible following efalizumab clearance. Efalizumab treatment also resulted in a marked increase in the blood of CD8+ memory cells, a T-cell population that is selectively increased in psoriatic lesions, suggesting re trafficking or blocked tissue entry of a disease-relevant population in psoriasis. Naïve, but not effector, CD8+ T cells were also increased in the blood, consistent with reduced entry into lymph nodes. Fluorescence-activated cell sorter analyses of peripheral blood mononuclear cells confirmed the down-modulation of CD11a and CD18, the α - and β -chains of LFA-1, on CD3+ cells. In addition, other adhe-

sion molecules including very late antigen 4, β 7-integrin and to some extent CD11b and L-selectin were also down-regulated. However, CD11c, CD44 and cutaneous lymphocyte antigen were not down-regulated. The down-modulation of these adhesion molecules likely contributes to the anti-adhesive effect of efalizumab. A number of in vitro studies have characterized the multiple effects of efalizumab. Experiments with human umbilical vein endothelial cells (HUVECs) in vitro have demonstrated that efalizumab inhibits transendothelial trafficking of T cells in a concentration-dependent manner (fig. 4)⁶, consistent with the hypothesis that efalizumab inhibits trafficking of T cells from blood vessels into the skin. Efalizumab also inhibits binding of the human Jurkat T cells to normal human keratinocytes [44], inhibits lymphocyte proliferation in a mixed lymphocyte reactions assay and binds to lymphocytes at therapeutic concentrations achieved in the phase III studies. Collectively, these data indicate that efalizumab is a promising anti-adhesion antibody for the treatment of psoriasis [50].

Results of a histological analysis of lesional tissue (study HUPS254) indicated a significant decrease in mean epidermal thickness in the majority of efalizumab-treated patients with a mean decrease in epidermal thickness of 22 and 40% on days 28 and 56, respectively [Genentech Inc., data on file]. Additionally, on day 28 mean T-cell counts decreased by 44 and 52% in the epidermis and dermis, respectively, and by 63% in both the epidermis and dermis on day 56. A reduction in CD11a binding sites was observed in all patients on day 56, with complete blockade observed in 46% of patients. Thirty-five percent of patients exhibited greatly reduced keratin 16 expression in suprabasal keratinocytes on day 56, indicating normalization of keratinocyte maturation and differentiation. The histological responses following 12 weeks of efalizumab treatment from an additional study (study HUPS256) supported these findings [Genentech Inc., data on file]. On day 84, the mean decrease in epidermal thickness was 48%. The mean decrease in epidermal and dermal T-cell counts was 78 and 70%, respectively, and complete CD11a blockade was observed in 82% of patients. Forty-six percent of patients had no expression of keratin 16 in suprabasal keratinocytes, indicating complete resolution of psoriatic disease, and 39% of patients did not express ICAM-1.

³ Gottlieb AB, Hamilton TK, Walicke PA, Li N, Joshi A, Garovoy M, Gordon KB: Efficacy, safety, and pharmacokinetic outcomes observed in patients with plaque psoriasis during long-term efalizumab therapy: Results from an open-label trial. *Int Invest Dermatol Meet*, Miami Beach, 2003, poster 1247.

⁴ Mortensen DL, et al: *Int Invest Dermatol Meet*, Miami Beach, 2003, poster 379.

⁵ Vugmeyster Y, Howell K, Kikuchi T, et al: Efalizumab modulates an array of adhesion-related and activation-controlling surface protein on T lymphocytes and inhibits anti-CD3-induced T-cell activation in adults with moderate to severe psoriasis. *Int Invest Dermatol Meet*, Miami Beach, 2003, poster 47.

⁶ Lowe J, Stefanich E, Rangell L, Pippig S: Efalizumab (anti-CD11a) inhibits transendothelial migration of T cells. *Poster Soc Invest Dermatol Meet*, Los Angeles, 2002.

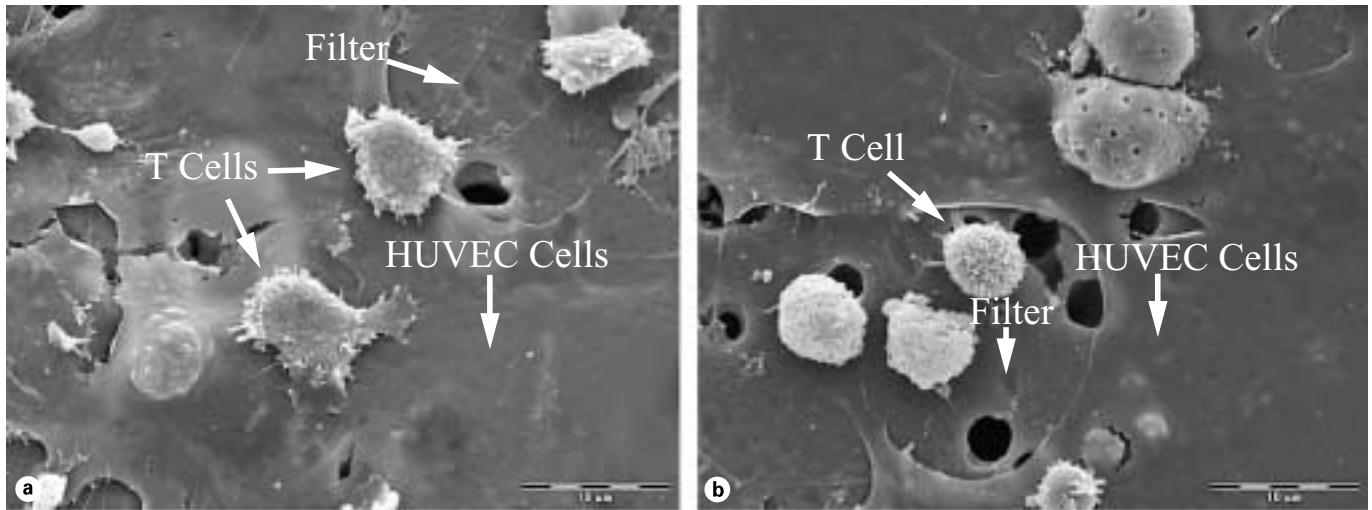


Fig. 4. Inhibition of T-cell transendothelial trafficking with efalizumab. Activated human T cells were pre-incubated in the absence and presence of $\pm 10 \mu\text{g/ml}$ efalizumab and added to the HUVEC-coated upper well of a transwell assay system. The chemokine rhuSDF-1 α /PBSF was added to the lower well, and the T cells were allowed to transmigrate for 2.5 h. Shown are scanning electron microscopy illus-

trations of HUVEC-coated wells with T cells that had not been **(a)** or had been **(b)** pre-incubated with efalizumab. Photos **a** and **b** demonstrate that more T cells adhered to HUVECs in the absence than in the presence of $10 \mu\text{g/ml}$ efalizumab. Whereas T cells spread out on HUVECs in the absence of efalizumab **(a)**, most cells retained their round shape in the presence of efalizumab **(b)**.

A phase III randomized, double-blind, placebo-controlled multicentre clinical trial (ACD2390g) investigated the repeated weekly administration of subcutaneous efalizumab (1 mg/kg/week) [C.L. Leonardi, unpubl. data]. Pharmacodynamic assessment in patients treated in this phase III study showed results similar to previous phase I studies with efalizumab. There was a reduction in CD11a expression on circulating T lymphocytes to approximately 15–30% of baseline, and CD11a binding sites were generally more than 95% saturated. Mean leucocyte counts increased 40% from baseline, and mean lymphocyte proportions increased 60% from baseline, all remaining within the normal range. Monocyte and neutrophil proportions showed little change, and there was no depletion of any WBC population during efalizumab therapy.

Preliminary results are available from an ongoing open-label extended treatment trial in which patients received subcutaneous efalizumab (2 mg/kg/week) for 12 weeks, followed by up to 33 months of maintenance therapy with efalizumab (1 mg/kg/week , dose increased to 2–4 mg/kg/week as necessary), for patients who achieved at least 50% improvement in the Psoriasis Area and Severity Index (PASI), or a static Physician Global Assessment (sPGA) rating of clear, minimal or mild [47]. Pharmacokinetic analysis of each 12-week treatment period for up to 15 months revealed no evidence of additional efalizu-

mab accumulation or alteration of the pharmacokinetic profile during long-term treatment.

Efalizumab Provides Clinical Efficacy and Is Well Tolerated in Patients with Moderate to Severe Chronic Plaque Psoriasis

Multiple phase III studies conducted in approximately 1,650 patients have determined the efficacy and safety of efalizumab for the treatment of moderate to severe chronic plaque psoriasis [51, 52]. In a pooled analysis of the first 12 weeks of therapy for 3 trials, significantly more efalizumab-treated patients achieved a $\geq 75\%$ decrease in the PASI (PASI-75) and PASI-50 compared to placebo. Significantly more efalizumab-treated patients demonstrated improvement on all efficacy end points relative to placebo⁷. Consistent with the time frame of T-cell modulation, efalizumab provided rapid improvement in psoriasis, with a significantly greater percent PASI improvement versus placebo observed after only 2 weeks of treatment ($p < 0.0001$).

⁷ Ouellet JP, Toth DP, Gratton D: Efalizumab provides rapid onset of clinical benefit in patients with moderate to severe plaque psoriasis (abstract). *J Eur Acad Dermatol Venereol* 2003;17:371.

Adverse events were generally mild to moderate. The most frequently reported events were acute adverse events (predefined during the trials as headache, chills, nausea, fever, myalgia and vomiting that occurred on the day of the dose or on either of 2 days following the dose) following the first 1 or 2 injections of efalizumab. By the third and all subsequent doses, the incidence was comparable between the efalizumab and placebo groups. Acute adverse events were not treatment limiting, with less than 1% of patients discontinuing efalizumab due to such events. Efalizumab was not associated with T-cell depletion, increased rate of infection or malignancy, or hepatotoxicity or nephrotoxicity⁸. During the efalizumab clinical trials programme, 8 of 2,762 patients (0.3%) developed thrombocytopenia; therefore, platelet monitoring is recommended. As worsening of psoriasis or new morphologies may occur during or more commonly following efalizumab discontinuation, appropriate psoriasis treatment is recommended.

Conclusion

The rapid expansion in knowledge of the immunopathogenesis of psoriasis has led to the development of targeted biological agents, offering much hope for improved therapies for this incurable skin disease. Some biological agents in development for psoriasis are single-target agents that may not necessarily lead to a significant clinical improvement [53]. Agents such as efalizumab, which target multiple stages in the psoriasis disease process, may prove to be more effective. Efalizumab targets psoriasis pathogenesis at multiple levels, inhibiting T-cell activation in the lymph nodes and binding of T cells to endothelial cells, blocking trafficking of T cells from the circulation into the skin, and preventing reactivation of T cells in the dermal and epidermal tissues.

Consistent with its proposed mechanism of action, efalizumab causes rapid down-modulation of CD11a and saturation of CD11a binding sites on the surface of circulating T lymphocytes, as well as in the dermis and epidermis of psoriatic lesions. This is accompanied by an increase in the level of circulating lymphocytes, remaining within normal limits, and a decrease in T-cell number

in the dermis and epidermis, most likely reflecting a reduction in T-cell trafficking into the skin. The reduction in keratin 16 and ICAM-1 expression in keratinocytes suggests that efalizumab can reverse the histological evidence of inflammation and epidermal hyperplasia. These effects of efalizumab on circulating T cells and skin histology are accompanied by significant clinical improvements on multiple efficacy measures (PASI, sPGA). No depletion of lymphocytes has been reported with repeated efalizumab use, and any observed elevation in WBC subpopulations was fully reversible, with a return to pretreatment levels 7–10 days following clearance of efalizumab from the circulation. Several ongoing studies are investigating the long-term pharmacodynamic and histological effects of efalizumab following continuous repeated administration. Preliminary results from these studies indicate that efalizumab provides continuous control of psoriasis symptoms without an increased risk of toxicity⁹. Collectively, these data indicate that efalizumab may be an important option for dermatologists seeking to provide a well-tolerated and effective treatment modality for their patients with moderate to severe chronic plaque psoriasis.

Acknowledgments

The data presented herein are derived from clinical trials sponsored by Genentech Inc. and XOMA (US) LLC, who codeveloped efalizumab; both companies conducted clinical trials. The authors gratefully acknowledge the contribution of Kirsten Duncan, PharmD, to the development of this paper.

⁸ Rosoph L: Safety of efalizumab, a humanized monoclonal antibody, in patients with moderate to severe plaque psoriasis (abstract). *J Eur Acad Dermatol Venereol* 2003;17:371.

⁹ Gottlieb AB, et al: Efficacy, safety and pharmacokinetic outcomes observed in patients with plaque psoriasis during long-term efalizumab therapy: Results from an open-label trial. *Int Invest Dermatol Meet*, Miami Beach, 2003, poster 1247.

References

- 1 Austin LM, Ozawa M, Kikuchi T, Walters IB, Krueger JG: The majority of epidermal T cells in psoriasis vulgaris lesions can produce type 1 cytokines, interferon-gamma, interleukin-2, and tumor necrosis factor-alpha, defining TC1 (cytotoxic T lymphocyte) and TH1 effector populations: A type 1 differentiation bias is also measured in circulating blood T cells in psoriatic patients. *J Invest Dermatol* 1999;113:752-759.
- 2 Bos JD, Hulsebosch HJ, Krieg SR, Bakker PM, Cormane RH: Immunocompetent cells in psoriasis: In situ immunophenotyping by monoclonal antibodies. *Arch Dermatol Res* 1983;275:181-189.
- 3 Ferenczi K, Burack L, Pope M, Krueger JG, Austin LM: CD69, HLA-DR and the IL-2R identify persistently activated T cells in psoriasis vulgaris lesional skin: Blood and skin comparisons by flow cytometry. *J Autoimmun* 2000;14:63-78.
- 4 Lebwohl M, Ellis C, Gottlieb A, Koo J, Krueger G, Linden K, Shupack J, Weinstein G: Cyclosporine consensus conference: With emphasis on the treatment of psoriasis. *J Am Acad Dermatol* 1998;39:464-475.
- 5 Nicolas JF, Chamchick N, Thivolet J, Wijdenes J, Morel P, Revillard JP: CD4 antibody treatment of severe psoriasis. *Lancet* 1991;338:321.
- 6 Prinz J, Braun-Falco O, Meurer M, Daddona P, Reiter C, Rieber P, Riethmuller G: Chimaeric CD4 monoclonal antibody in treatment of generalised pustular psoriasis. *Lancet* 1991;338:320-321.
- 7 Gottlieb SL, Gilleaudeau P, Johnson R, Estes L, Woodworth TG, Gottlieb AB, Krueger JG: Response of psoriasis to a lymphocyte-selective toxin (DAB389IL-2) suggests a primary immune, but not keratinocyte, pathogenic basis. *Nat Med* 1995;1:442-447.
- 8 Gilhar A, David M, Ullmann Y, Berkutski T, Kalish RS: T-lymphocyte dependence of psoriatic pathology in human psoriatic skin grafted to SCID mice. *J Invest Dermatol* 1997;109:283-288.
- 9 Wrone-Smith T, Nickoloff BJ: Dermal injection of immunocytes induces psoriasis. *J Clin Invest* 1996;98:1878-1887.
- 10 Krueger JG: The immunologic basis for the treatment of psoriasis with new biologic agents. *J Am Acad Dermatol* 2002;46:1-23.
- 11 Cameron AL, Kirby B, Fei W, Griffiths CE: Natural killer and natural killer-T cells in psoriasis. *Arch Dermatol Res* 2002;294:363-369.
- 12 Nickoloff BJ: The immunologic and genetic basis of psoriasis. *Arch Dermatol* 1999;135:1104-1110.
- 13 Bonish B, Jullien D, Dutronc Y, Huang BB, Modlin R, Spada FM, Porcelli SA, Nickoloff BJ: Overexpression of CD1d by keratinocytes in psoriasis and CD1d-dependent IFN-gamma production by NK-T cells. *J Immunol* 2000;165:4076-4085.
- 14 Nickoloff BJ, Bonish B, Huang BB, Porcelli SA: Characterization of a T cell line bearing natural killer receptors and capable of creating psoriasis in a SCID mouse model system. *J Dermatol Sci* 2000;24:212-225.
- 15 Bos JD, De Rie MA: The pathogenesis of psoriasis: Immunological facts and speculations. *Immunol Today* 1999;20:40-46.
- 16 Valdimarsson H, Baker BS, Jonsdottir I, Powles A, Fry L: Psoriasis: A T-cell-mediated autoimmune disease induced by streptococcal superantigens? *Immunol Today* 1995;16:145-149.
- 17 Robert C, Kupper TS: Inflammatory skin diseases, T cells, and immune surveillance. *N Engl J Med* 1999;341:1817-1828.
- 18 Delves PJ, Roitt IM: The immune system: Second of two parts. *N Engl J Med* 2000;343:108-117.
- 19 Grakoui A, Bromley SK, Sumen C, Davis MM, Shaw AS, Allen PM, Dustin ML: The immunological synapse: A molecular machine controlling T cell activation. *Science* 1999;285:221-227.
- 20 Springer TA, Dustin ML, Kishimoto TK, Marlin SD: The lymphocyte function-associated LFA-1, CD2, and LFA-3 molecules: Cell adhesion receptors of the immune system. *Annu Rev Immunol* 1987;5:223-252.
- 21 Malissen B: Dancing the immunological two-step. *Science* 1999;285:207-208.
- 22 Fuhlbrigge RC, King SL, Dimitroff CJ, Kupper TS, Sackstein R: Direct real-time observation of E- and P-selectin-mediated rolling on cutaneous lymphocyte-associated antigen immobilized on Western blots. *J Immunol* 2002;168:5645-5651.
- 23 Homey B, Alenius H, Muller A, Soto H, Bowman EP, Yuan W, McEnvoy L, Lauerman AI, Assmann T, Bunemann E, Lehto N, Wolff H, Yen D, Marxhausen H, To W, Sedgwick J, Ruzicka T, Lehmann P, Zlotnik A: CCL27-CCR10 interactions regulate T cell-mediated skin inflammation. *Nat Med* 2002;8:157-165.
- 24 Bradley LM, Watson SR: Lymphocyte migration into tissue: The paradigm derived from CD4 subsets. *Curr Opin Immunol* 1996;8:312-320.
- 25 Chang JCC, Smith LR, Froning KJ, Schwabe BJ, Laxer JA, Caralli LL, Kurland HH, Karasek MA, Wilkinson DI, Carlo DJ, Brostoff SW: CD8+ T cells in psoriatic lesions preferentially use T-cell receptor V beta 3 and/or V beta 13.1 genes. *Proc Natl Acad Sci USA* 1994;91:9282-9286.
- 26 Messen A, Trommler P, Vollmer S, Schendel D, Albert E, Gurtler L, Riethmuller G, Prinz JC: Evidence for an antigen-specific cellular immune response in skin lesions of patients with psoriasis vulgaris. *J Immunol* 1995;155:4078-4083.
- 27 Vollmer S, Messen A, Trommler P, Schendel D, Prinz JC: T lymphocytes derived from skin lesions of patients with psoriasis vulgaris express a novel cytokine pattern that is distinct from that of T helper type 1 and T helper type 2 cells. *Eur J Immunol* 1994;24:2377-2382.
- 28 Cella M, Scheidegger D, Palmer-Lehmann K, Lane P, Lanzavecchia A, Alber G: Ligation of CD40 on dendritic cells triggers production of high levels of interleukin-12 and enhances T cell stimulatory capacity: T-T help via APC activation. *J Exp Med* 1996;184:747-752.
- 29 Caux C, Massacrier C, Vanbervliet B, Dubois B, van Kooten C, Durand I, Banchereau J: Activation of human dendritic cells through CD40 cross-linking. *J Exp Med* 1994;180:1263-1272.
- 30 Sallusto F, Lanzavecchia A: Efficient presentation of soluble antigen by cultured human dendritic cells is maintained by granulocyte/macrophage colony-stimulating factor plus interleukin 4 and downregulated by tumor necrosis factor alpha. *J Exp Med* 1994;179:1109-1118.
- 31 Nickoloff BJ, Griffiths CE, Barker JN: The role of adhesion molecules, chemotactic factors, and cytokines in inflammatory and neoplastic skin disease -1990 update. *J Invest Dermatol* 1990;94:151S-157S.
- 32 Groves RW, Ross E, Barker JN, Ross JS, Camp RD, MacDonald DM: Effect of in vivo interleukin-1 on adhesion molecule expression in normal human skin. *J Invest Dermatol* 1992;98:384-387.
- 33 Ovigne JM, Baker BS, Brown DW, Powles AV, Fry L: Epidermal CD8+ T cells in chronic plaque psoriasis are Tc1 cells producing heterogeneous levels of interferon-gamma. *Exp Dermatol* 2001;10:168-174.
- 34 Bata-Csorgo Z, Hammerberg C, Voorhees JJ, Cooper KD: Kinetics and regulation of human keratinocyte stem cell growth in short-term primary ex vivo culture: Cooperative growth factors from psoriatic lesional T lymphocytes stimulate proliferation among psoriatic uninvolved, but not normal, stem keratinocytes. *J Clin Invest* 1995;95:317-327.
- 35 Prinz JC, Gross B, Vollmer S, Trommler P, Strobel I, Meurer M, Plewig G: T cell clones from psoriasis skin lesions can promote keratinocyte proliferation in vitro via secreted products. *Eur J Immunol* 1994;24:593-598.
- 36 Krensky AM, Sanchez-Madrid F, Robbins E, Nagy JA, Springer TA, Burakoff SJ: The functional significance, distribution, and structure of LFA-1, LFA-2, and LFA-3: Cell surface antigens associated with CTL-target interactions. *J Immunol* 1983;131:611-616.
- 37 Benjamin RJ, Qin SX, Wise MP, Cobbold SP, Waldmann H: Mechanisms of monoclonal antibody-facilitated tolerance induction: A possible role for the CD4 (L3T4) and CD11a (LFA-1) molecules in self-non-self discrimination. *Eur J Immunol* 1988;18:1079-1088.
- 38 Fischer A, Durandy A, Sterkers G, Griscelli C: Role of the LFA-1 molecule in cellular interactions required for antibody production in humans. *J Immunol* 1986;136:3198-3203.
- 39 de Fougerolles AR, Qin X, Springer TA: Characterization of the function of intercellular adhesion molecule (ICAM)-3 and comparison with ICAM-1 and ICAM-2 in immune responses. *J Exp Med* 1994;179:619-629.

- 40 Tanaka Y, Takahashi A, Arai I, Inoue T, Higuchi S, Otomo S, Watanabe K, Habu S, Nishimura T: Prolonged inhibition of an antigen-specific IgE response in vivo by monoclonal antibody against lymphocyte function-associated antigen-1. *Eur J Immunol* 1995;25:1555–1558.
- 41 Hamann A, Jablonski-Westrich D, Duijvestijn A, Butcher EC, Baisch H, Harder R, Thiele HG: Evidence for an accessory role of LFA-1 in lymphocyte-high endothelium interaction during homing. *J Immunol* 1988;140:693–699.
- 42 Issekutz TB: Inhibition of lymphocyte endothelial adhesion and in vivo lymphocyte migration to cutaneous inflammation by TA-3, a new monoclonal antibody to rat LFA-1. *J Immunol* 1992;149:3394–3402.
- 43 Dustin ML, Springer TA: Lymphocyte function-associated antigen-1 (LFA-1) interaction with intercellular adhesion molecule-1 (ICAM-1) is one of at least three mechanisms for lymphocyte adhesion to cultured endothelial cells. *J Cell Biol* 1988;107:321–331.
- 44 Werther WA, Gonzalez TN, O'Connor SJ, McCabe S, Chan B, Hotaling T, Champe M, Fox JA, Jardieu PM, Berman PW, Presta LG: Humanization of an anti-lymphocyte function-associated antigen (LFA)-1 monoclonal antibody and reengineering of the humanized antibody for binding to rhesus LFA-1. *J Immunol* 1996;157:4986–4995.
- 45 Gottlieb A, Krueger JG, Bright R, Ling M, Lebowhl M, Kang S, Feldman S, Spellman M, Wittkowski K, Ochs HD, Jardieu P, Bauer R, White M, Dedrick R, Garovoy M: Effects of administration of a single dose of a humanized monoclonal antibody to CD11a on the immunobiology and clinical activity of psoriasis. *J Am Acad Dermatol* 2000;42:428–435.
- 46 Gottlieb AB, Krueger JG, Wittkowski K, Dedrick R, Walicke PA, Garovoy M: Psoriasis as a model for T-cell-mediated disease: Immunobiologic and clinical effects of treatment with multiple doses of efalizumab, an anti-CD11a antibody. *Arch Dermatol* 2002;138:591–600.
- 47 Gottlieb AB, Miller B, Lowe N, Shapiro W, Hudson C, Bright R, Ling M, Magee A, McCall CO, Rist T, Dummer W, Walicke P, Bauer RJ, White M, Garovoy M: Subcutaneously administered efalizumab (anti-CD11a) improves signs and symptoms of moderate to severe plaque psoriasis. *J Cutan Med Surg* 2003;7:198–207.
- 48 Papp K, Bissonnette R, Krueger JG, Carey W, Gratton D, Gulliver WP, Lui H, Lynde CW, Magee A, Minier D, Ouellet JP, Patel P, Shapiro J, Shear NH, Kramer S, Walicke P, Bauer R, Dedrick RL, Kim SS, White M, Garovoy MR: The treatment of moderate to severe psoriasis with a new anti-CD11a monoclonal antibody. *J Am Acad Dermatol* 2001;45:665–674.
- 49 Bauer RJ, Dedrick RL, White ML, Murray MJ, Garovoy MR: Population pharmacokinetics and pharmacodynamics of the anti-CD11a antibody hu1124 in human subjects with psoriasis. *J Pharmacokinet Biopharm* 1999;27:397–420.
- 50 Dedrick RL, Walicke P, Garovoy M: Anti-adhesion antibodies efalizumab, a humanized anti-CD11a monoclonal antibody. *Transpl Immunol* 2002;9:181–186.
- 51 Gordon KB, Papp KA, Hamilton TK, Walicke PA, Dummer W, Li N, Breshnahan BW, Menter A, Efalizumab Study Group: Efalizumab for patients with moderate to severe plaque psoriasis: A randomized controlled trial. *JAMA* 2003;290:3073–3080.
- 52 Lebowhl M, Tying SK, Hamilton TK, Toth D, Glazer S, Tawfik NH, Walicke P, Dummer W, Wang X, Garovoy MR, Pariser D, Efalizumab Study Group: A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. *N Engl J Med* 2003;349:2004–2013.
- 53 Mrowietz U: Advances in systemic therapy for psoriasis. *Clin Exp Dermatol* 2001;26:362–367.