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

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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.

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 DAB_{389}IL-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.

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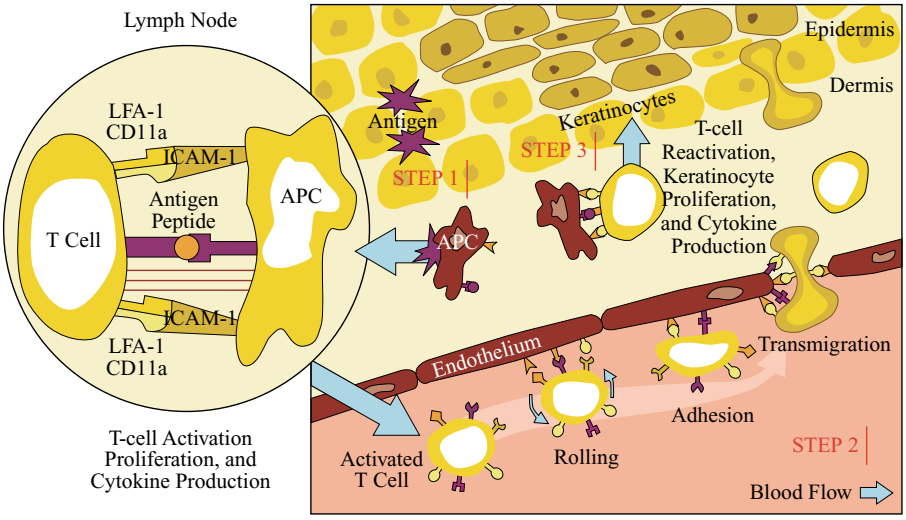

Fig. 1. Key T-cell interactions in the pathogenesis of psoriasis. In order to mediate the cellular changes in the dermis that lead to psoriasis, T cells first undergo 3 key interactions with other cell types. Step 1: APCs must first be activated in the epidermis, where antigen is internalized, enzymatically 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 tonsils[1], 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.

[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.

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,

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

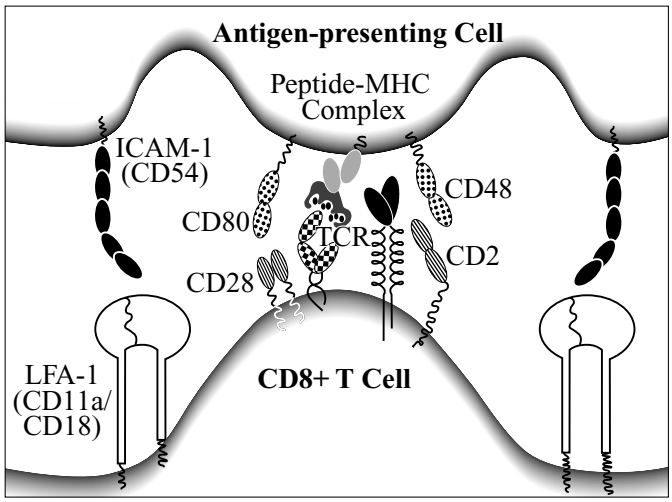

Fig. 2. Formation of the immunological synapse. Reprinted with permission from Elsevier [van der Merwe PA, Barclay AN: Trends Biochem Sci 1994;19:354–358], adapted by Malissen [21].

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-

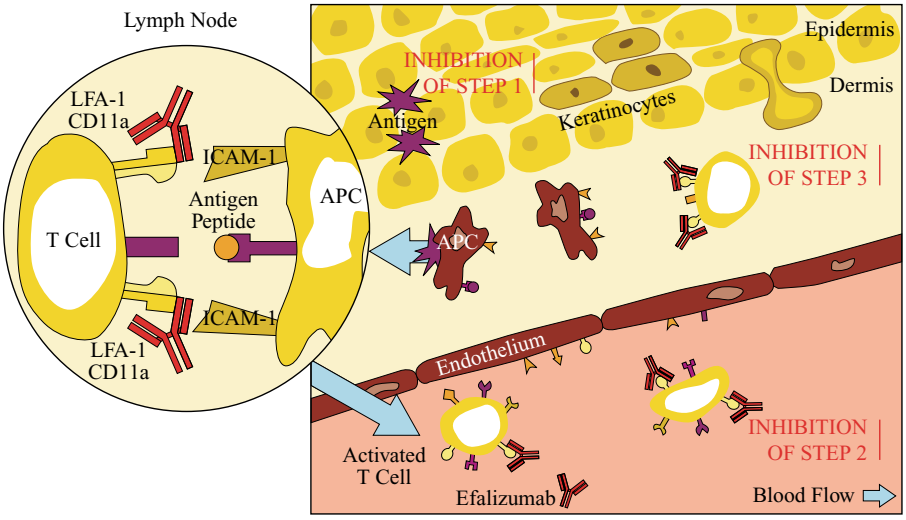

Fig. 3. Efalizumab mechanisms of action. Efalizumab inhibits adhesion of T cells to other cell types by inhibiting the binding of LFA-1 to ICAM-1. This mechanism of action has a number of effects, depending on the cell type, including inhibition of T-cell activation, inhibition of T-cell trafficking 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 suprabasal keratinocytes, whereas in homoeostatic 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 studies[3] [XOMA (US) LLC and Genentech Inc., data on file].

Following efalizumab treatment of 1 mg/kg/week for 12 weeks[4], 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 retrafficking 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 adhesion molecules including very late antigen 4, β7-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.

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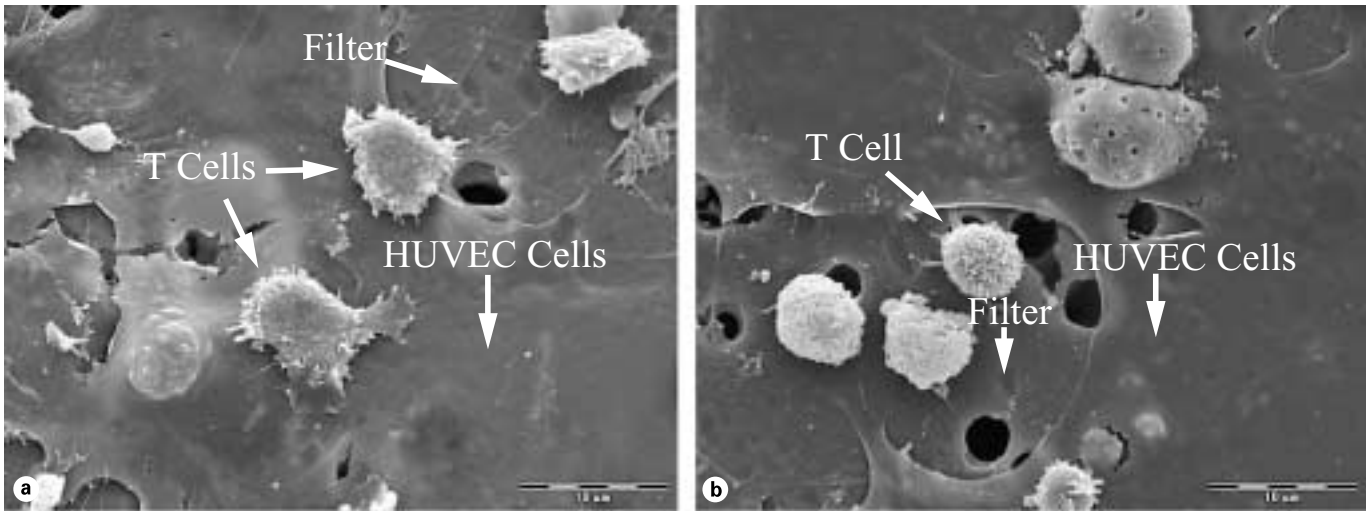

Fig. 4. Inhibition of T-cell transendothelial trafficking with efalizumab. Activated human T cells were pre-incubated in the absence and presence of ± 10 μg/ml efalizumab and added to the HUVEC-coated upper well of a transwell assay system. The chemokine rhuSDF-1 α/PBSF was added to the lower well, and the T cells were allowed to transmigrate for 2.5 h. Shown are scanning electron microscopy illustrations 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 μg/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 efalizumab 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 ≥ 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 placebo[7]. 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 nephrotoxicity[8]. 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 toxicity[9]. 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.

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