Psoriasis as a Model for T-Cell–Mediated Disease

Immunobiologic and Clinical Effects of Treatment With Multiple Doses of Efalizumab, an Anti–CD11a Antibody

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Background: Leukocyte function–associated antigen 1 (LFA-1), consisting of CD11a and CD18 subunits, plays an important role in T-cell activation and leukocyte extravasation.

Objective: To test whether blocking CD11a decreases immunobiologic and clinical activity in psoriatic plaques.

Design: Open-label, multicenter, dose escalation study.

Patients: Thirty-nine patients with moderate-to-severe psoriasis.

Intervention: Intravenous infusions of efalizumab, a humanized anti-CD11a monoclonal antibody, for 7 weeks at doses of 0.1 mg/kg every other week or 0.1 mg/kg weekly (category 1), 0.3 mg/kg weekly (category 2), and 0.3 increasing to 0.6 or 1.0 mg/kg weekly (category 3). Skin biopsies were performed on days 0, 28, and 56.

Main Outcome Measures: Serum efalizumab levels, levels of total and unoccupied T-cell CD11a, T cell counts, epidermal thickness, cutaneous intercellular adhesion molecule 1 (ICAM-1) and keratin 16 (K16) expression, Psoriasis Area and Severity Index (PASI) scores.

Results: Dose-response relationships were observed for pharmacokinetics and pharmacodynamic measures. Category 1 failed to maintain detectable serum efalizumab or T cell CD11a down-modulation between doses. Category 2 achieved both. Category 3 achieved both and additionally maintained sustained T-cell CD11a saturation between doses. A dose-response relationship was also observed clinically and histologically. The mean decrease in the PASI score was 47% in category 3, 45% in category 2, and 10% in category 1 (P<.001). Epidermal and dermal T-cell counts, epidermal thickness, and ICAM-1 and K16 expression decreased in categories 2 and 3 but not in category 1. Circulating lymphocyte counts increased in categories 2 and 3.

Conclusions: At doses of 0.3 mg/kg or more per week, intravenous efalizumab produced significant clinical and histologic improvement in psoriasis, which correlated with sustained serum efalizumab levels and T-cell CD11a saturation and down-modulation.

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INTERCELLULAR ADHESION molecules (ICAMs) facilitate the binding of antigen-presenting cells and keratinocytes to T cells and are thought to provide costimulatory signals necessary for T-cell activation.1 Interactions among cellular adhesion molecules also facilitate the continuous recirculation of T lymphocytes among lymph nodes, tissues, and blood.2 Leukocyte function–associated antigen 1 (LFA-1) is a member of the leukocyte β2-integrin family of adhesion molecules, characterized by heterodimers with a common β chain (CD18) and a unique α chain (CD11a for LFA-1).3 Expression of LFA-1 is restricted to leukocytes. A receptor for LFA-1, ICAM-1, can be expressed on a variety of cells, including T lymphocytes, endothelial cells, and epidermal keratinocytes.4 Expression of ICAM-1 is coordinated with the progression of local immune responses, and its induction in inflammation is an important means of regulating LFA-1/ICAM-1 interactions.5 Antibodies to LFA-1 or its ligands that interfere with the LFA-1/ICAM adhesion mechanism attenuate a broad range of T-cell–mediated reactions in vitro and in animal models.6,7 CD11a blockade is predicted to produce less global immune suppression compared with CD18 blockade because T cells are relatively dependent on CD11a/CD18 (LFA-1) compared with other types of leukocytes.1

Psoriasis is an inflammatory disease characterized by hyperproliferation of keratinocytes and accumulation of activated T cells in the epidermis and dermis.
PATIENTS, MATERIALS, AND METHODS

STUDY DRUG

Efalizumab (Xanelim; Genentech, Inc, or hu1124) is a humanized IgG1 version of the murine anti-human CD11a monoclonal antibody MHM24, generated by grafting the MHM24 complementarity determining regions into consensus human IgG1 κ heavy and light chain sequences.26

PATIENT POPULATION

The study population consisted of patients with stable, moderate-to-severe plaque psoriasis (defined as >15% body surface area involvement and a PASI score ≥13.0). Patients discontinued treatment with psoralen–UV-A and systemic antipsoriatic therapies for at least 28 days before study drug administration. Prescription topical therapies and use of UV-B were discontinued for at least 2 weeks before study drug administration.

TRIAL DESIGN

This was an open-label, multiple-dose, dose escalation, 8-center, phase 1/2 study. The study was conducted in accordance with the Declaration of Helsinki. Subjects sequentially received the following dose levels in an ascending dose escalation paradigm: 0.1 mg/kg every other week (group A); 0.1 mg/kg weekly (group B); 0.3 mg/kg weekly (group C); 0.3, 0.4, then 0.6 mg/kg for the remaining weeks (group D); and 0.3, 0.4, 0.6, then 1.0 mg/kg for the remaining weeks (group E). The intrasubject dose escalation in groups D and E was performed because the prior phase 1/2 study25 demonstrated that initial doses of more than 0.3 mg/kg were accompanied by more frequent infusion-related adverse events.

Subjects were seen at least weekly during the treatment phase and were followed up for a minimum of 98 days (56 days after the last dose). Efficacy was monitored weekly by the PASI.27 This study was a phase 1/2 study and did not have a formal primary end point at a predetermined time point. However, the main analysis of efficacy was performed 1 week after the last dose (day 56). Biologic activity was also assessed by histologic analysis of skin biopsy specimens obtained at baseline, day 28, and day 56 from the same area of plaque. Safety was assessed by adverse events, clinical laboratory assessments (including blood chemical analysis, hematologic analysis, and urinalysis), pretreatment and posttreatment physical examinations (including vital signs), and human antihumanized antibody tests. Additional clinical immunology test results were examined, specifically cutaneous cell-mediated immune reaction to tetanus, mumps, or Candida antigens and secondary humoral antibody response to tetanus toxoid.

HISTOLOGIC METHODS

ON CRYOSTAT SKIN SECTIONS

Immunohistochemical analysis for CD11a was performed with biotinylated efalizumab (hu1124) and clone 25.3 (Beckman Coulter, Inc, Miami, Fla), another CD11a antibody that binds to a noncompeting epitope on CD11a. Determination of epidermal thickness, numbers of epidermal CD3+ and CD11a+ T cells, and keratinocyte ICAM-1 and keratin 16 (K16) expression were performed of psoriatic lesions.15-20 Evidence indicates that T cells play a key role in the pathogenesis of psoriasis.17-23 Up-regulation of ICAM-1 expression in psoriatic plaques may facilitate T-cell extravasation, adhesion to keratinocytes, and activation of T lymphocytes through interaction with LFA-1.21,24 Therefore, inhibition of the ICAM-1/LFA-1 adhesion interaction may decrease clinical activity in psoriatic plaques.

In a previous open-label study,25 patients with moderate-to-severe psoriasis received a single dose of intravenous efalizumab, ranging from 0.03 to 10 mg/kg. Although this single dose produced only a transient blockade of lymphocyte CD11a, the mean decrease in Psoriasis Area and Severity Index (PASI) scores 28 days later was 33% in 15 of 31 responding patients. Clinical response was accompanied by decreased numbers of epidermal CD3+ T cells, reduced CD11a levels on T cells, decreased keratinocyte and blood vessel expression of ICAM-1, epidermal thinning, and improved but not normalized keratinocyte differentiation. Adverse events were mild at doses of 0.3 mg/kg or less and included chills, abdominal discomfort, headache, and fever.

In the study reported herein, 39 patients with moderate-to-severe psoriasis were treated with multiple, intravenous doses of efalizumab for 7 weeks. Dose-response relationships were examined for pharmacokinetic, pharmacodynamic, and histologic and clinical psoriasis measures.

RESULTS

PATIENT DEMOGRAPHICS

A total of 39 subjects (age range, 26-73 years) were enrolled at 8 study centers (Figure 1). The median baseline PASI score was 23 (range, 15-42). One subject in group C discontinued treatment after the first dose of efalizumab because of headache and fever. All of the remaining subjects completed the treatment portion of the study, but 4 subjects did not complete the follow-up period. Three withdrew because of worsening psoriasis and 1 was lost to follow-up. Pharmacokinetic, hematologic, and clinical results are reported using data available at each time point for the entire cohort of 39 subjects. However, because of early discontinuations or damage to some biopsy samples during transit, histologic analyses were conducted only for 32 subjects. Therefore, only 32 patients constituted the fully evaluable subgroup for comparisons among laboratory, histologic, and clinical outcomes.

PHARMACOKINETICS OF EFALIZUMAB

Group geometric mean plasma concentrations are indicated by the dotted line graphs in Figure 2A; concentrations are indicated on the logarithmic y-axis. In dose...


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and E. Full recovery of CD11a expression occurred 70% to 80% throughout the treatment in groups C, D, T-cell surface CD11a remained down-modulated by baseline between infusions in group B. In contrast, next dose and partially recovered to within 30% of recovered to pretreatment levels in group A before the lizumab concentration. Surface CD11a expression Figure 2A shows mean surface CD11a expression com-

25.3, therefore, reflects down-modulation of CD11a. Plasma efalizumab levels were measured by enzyme-linked immunosorbent assay (ELISA) as previously de-
scribed.25,28 Limit of detection was 25 ng/mL of efali-

zumab. Antibody to efalizumab (hu1124) was determined using a double-antigen sandwich ELISA as previously de-
scribed.28 The detection limit was approximately 5 ng/mL. Flow cytometry of circulating T cells was performed using a FACScan flow cytometer (Becton Dickinson and Co, San Jose, Calif). Lymphocytes were identified by forward and side scatter characteristics. T cells were identified by binding to CD1 and fluorescein isothiocyanate (FITC) anti-CD3. Reduction in cell surface expression of CD11a (down-modulation) on circulating CD3+ T cells was monitored with a FITC anti-CD11a (clone 25.3; Beckman Coulter, Inc), as previously described.29 Saturation of efalizumab (hu1124) on circulating T cells was determined by comparing the amount of bound drug to the total amount that could bind at saturation. Blood cells were washed to remove plasma components and un-
bound efalizumab (hu1124). The washed blood cells were incubated for 30 minutes at room temperature in the absence (bound) or presence (saturated) of 25 µg/mL of efalizumab (hu1124). The FITC-labeled goat F(ab')2 anti-
human IgG (Cappel; ICN Pharmaceuticals Inc, Aurora, Ohio) was used to detect efalizumab (hu1124) bound to the T-cell surface on flow cytometry. For each time point, the mean fluorescence intensity of the bound test was subtracted from the mean fluorescence intensity of the saturated test to generate a measure of available binding sites for efalizumab.

OTHER LABORATORY METHODS

Pharmacodynamics of Efalizumab

CD11a on the surface of circulating CD3+ T cells was measured by flow cytometry using an FITC-labeled monoclonal antibody (clone 25.3), whose binding is not inhibited by efalizumab. Decreased binding of FITC 25.3, therefore, reflects down-modulation of CD11a. Figure 2A shows mean surface CD11a expression com-
pared with the concurrent geometric mean plasma efali-

zumab concentration. Surface CD11a expression recovered to pretreatment levels in group A before the next dose and partially recovered to within 30% of baseline between infusions in group B. In contrast, T-cell surface CD11a remained down-modulated by 70% to 80% throughout the treatment in groups C, D, and E. Full recovery of CD11a expression occurred approximately 7 to 10 days after efalizumab was cleared from the plasma. When these data are compared with the pharmacokinetic results, it seems that down-

modulation is maintained only if plasma efalizumab remains at detectable levels throughout the interval between infusions. The 0.3-mg/kg weekly dose (group C) was the lowest dose that produced detectable efali-

zumab levels and maintained CD11a down-modulation throughout the treatment period.

The amount of LFA-1 (CD11a/CD18 heterodimer) available for biological function may depend both on the level of down-modulation (Figure 2A) and on the number of remaining CD11a molecules not occupied in vivo (Figure 2B). The amount of remaining, unbound surface CD11a (ie, still available for binding and bio-

logical activation) was determined by comparing the amount of efalizumab bound to lymphocytes harvested from treated patients to the maximum amount of efa-

lizumab that could be bound after further incubation in vitro with a saturating amount of drug (25 µg/mL). Fig-
ure 2B shows available CD11a relative to baseline on circulating CD3+ T cells during and after efalizumab treatment. In dose group A, available CD11a returned completely to pretreatment levels between doses. In dose group B (0.1 mg/kg weekly), available CD11a was decreased about 30%. In dose group C (0.3 mg/kg weekly), CD11a availability was largely suppressed, but

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of available binding sites remained, suggesting incomplete saturation with efalizumab. In the 2 highest-dose groups (D and E), available CD11a decreased to less than 5% of baseline levels, reflecting full down-modulation and high levels of saturation throughout treatment.

The patterns of efalizumab pharmacokinetics, CD11a down-modulation, and CD11a saturation divide the 5 dose groups into 3 categories. Category 1 (groups A and B) is defined by the failure to maintain detectable efalizumab serum levels and T-cell surface CD11a down-modulation between doses. Category 2 (group C) is characterized by sustained presence of detectable efalizumab and T-cell CD11a down-modulation, but failure to maintain CD11a saturation between doses. Category 3 (groups D and E) is characterized by sustained presence of detectable efalizumab and T-cell CD11a down-modulation and saturation between doses. These 3 dose categories will be used in the assessments of histologic and clinical outcomes.

HISTOLOGIC AND IMMUNOHISTOLOGIC EFFECTS OF EFALIZUMAB

T-cell decreases in the epidermis and dermis of psoriatic lesions occurred most consistently in subjects in categories 2 and 3 (Figure 3). For category 3 subjects, the median number of epidermal T cells decreased 70% and dermal T cells decreased 66% between baseline and day 56. The major portion of the decrease in both dermal and epidermal T-cell counts occurred between day 0 and day 28. The decrements observed for category 3 subjects at day 56 compared with day 0 were statistically significant for both dermal (P = .01) and epidermal (P = .047) T-cell counts. In category 2 subjects, only the decrement in epidermal T cells (P = .005) was significant at day 56. In contrast, changes in epidermal and dermal T-cell counts were not significant for category 1 subjects at either day 28 or day 56.

Histologic examinations of psoriatic skin revealed dose-dependent patterns of alteration in the availability of CD11a on cutaneous T cells (Table 1). Immunohistochemical analysis was performed with biotinylated efalizumab, providing an overall indication of CD11a availability on cutaneous T cells. Staining with biotinylated efalizumab was not changed at days 28 and 56 in 90% to 100% of the subjects in category 1. In contrast, 50% of category 2 and 100% of category 3 subjects had noticeably decreased staining on day 56. At day 28, 50% of category 2 subjects and 90% of category 3 subjects demonstrated no detectable staining with biotinylated efalizumab. The lower proportion of subjects negative for CD11a staining at day 56 may be related to poorer antibody penetration into skin as vascular abnormalities secondary to psoriasis resolve. When immunohistochemical analysis was performed with monoclonal antibody 25.3, which binds to a noncompeting epitope on CD11a, residual CD11a expression was detectable in all samples. These observations are similar to those for circulating T cells and indicate that CD11a can be both down-modulated and saturated with efalizumab on T cells in psoriatic plaques. However, as observed for circulating T cells, saturation of T-cell surface CD11a is not sustained as fully in category 2 as in category 3. Reductions in epidermal thickness across the 3 dose categories tended to parallel reductions in cutaneous T-cell infiltration and CD11a availability (Figure 3).

Keratinocyte expression of ICAM-1 and K16 is indicative of cytokine-mediated inflammation and aberrant maturation, respectively. There were no subjects in category 1 who became negative for ICAM or K16 expression during efalizumab treatment, and only 1 subject had a noticeable decrease in staining at day 56 (Table 1). In contrast, approximately 30% to 40% of subjects in categories 2 and 3 became negative for K16 at day 56. Additionally, K16 immunohistochemical staining was noticeably decreased in 50% of category 2 and 70% of category 3 subjects at day 56. Comparable, though somewhat less frequent, changes were observed in staining for ICAM. These observations demonstrate that efalizumab can reverse histologic evidence of inflammation and pathologic epidermal hyperplasia in psoriatic plaques.
Figure 2. Plasma efalizumab (hu1124) levels and down-modulation of T-cell CD11a (A) and available binding sites (eg, saturation) (B). CD11a expression on circulating T cells was measured by flow cytometry in blood samples collected just before infusion. Plasma efalizumab (hu1124) levels were measured by enzyme-linked immunosorbent assay in samples collected before and immediately after the 90-minute infusion. For plasma efalizumab levels, considerable variation was observed among subjects (more than a 30-fold difference in concentration at some time points). Therefore, the plasma efalizumab levels in A are expressed as the geometric mean (antilog of the mean of log [efalizumab]) (logarithmic y-axis; dotted lines). B, Group arithmetic means for T-cell surface CD11a were used because less intersubject variation was observed. These data are expressed as percentage of baseline value (linear y-axis; solid lines). Error bars indicate SEMs. Dose groups A through E correspond to those defined in Figure 1.
Overall, the data indicate that a relationship exists among plasma level of efalizumab, CD11a saturation and down-modulation, and histologic improvements (Table 2). Detectable plasma levels were not maintained between doses in category 1 but were maintained in categories 2 and 3. Trough levels were below the concentration needed to fully inhibit T-cell adhesion in in vitro assays for category 2 but not for category 3. Although all dose levels produced transient CD11a saturation and down-modulation, down-modulation was sustained only in categories 2 and 3, and CD11a saturation was sustained only in category 3. Changes in histologic variables of T-cell infiltration and epidermal thickness were not significant in category 1 but were evident in categories 2 and 3. These changes seemed to be more robust in category 3 subjects. Saturation of cutaneous T-cell CD11a was higher in category 3. Thus, it seems that a dose that maintains CD11a down-modulation is required for efficacy, and maintaining saturation of CD11a results in further increases in histologic improvement.

**EFALIZUMAB ADMINISTRATION–INDUCED SIGNIFICANT DISEASE IMPROVEMENT AS MEASURED BY PASI**

During treatment with efalizumab, the PASI score changed little for subjects in category 1 but decreased markedly for subjects in categories 2 and 3 (Figure 4). Changes in PASI scores seemed to be dose dependent, with the largest change observed in category 3 (representative response illustrated in Figure 5). There were individual patients who, after discontinuing therapy after 1 month and taking inadequate concentrations of efalizumab, worsened during the period of observation. Patients in category 3 experienced a mean decrease in PASI score from baseline of 47% at day 56 compared with 45% in category 2 and 10% in category 1 (P < .001).

**SAFETY AND IMMUNOLOGIC EVALUATION**

Safety information is provided for the entire cohort of 39 subjects who had any exposure to efalizumab. Drug-related adverse events were mostly mild or moderate in severity. The most common adverse events were fever (n = 20), headache (n = 12), chills (n = 9), nausea (n = 9), asthenia (n = 6), psoriasis (n = 8), and pharyngitis (n = 5). Fever and chills were reported more frequently in subjects receiving 0.3 mg/kg weekly or more of efalizumab than in subjects receiving 0.1 mg/kg weekly or less of efalizumab. The incidence was 62% vs 20% for fever and 28% vs 10% for chills in the 2 groups. These adverse events were particularly observed within 24 hours of the first dose of efalizumab and decreased on subsequent doses. Eight patients experience return of psoriasis during the posttreatment, observation phase. One subject experienced increased alkaline phosphatase levels that were severe and resolved within 2 months. Seven additional sub-
jects experienced elevated alanine aminotransferase (serum glutamic-pyruvic transaminase) and aspartate aminotransferase (serum glutamic-oxaloacetic transaminase) levels and elevated or decreased glucose levels; however, none was considered clinically significant by the investigators. No severe infections were noted in this study; the only noted malignancy was a non–drug-related basal cell carcinoma (in a patient with a history of PUVA therapy).

All but 2 subjects who were positive for tetanus antibody at screening retained their tetanus antibody response after repeated exposure to efalizumab. This indicates that an established IgG humoral antibody response persists following multiple doses of efalizumab. Measurement of cell-mediated immunity by administration of tetanus, mumps, and Candida antigens by skin testing showed persistence of cell-mediated immunity in 32 (89%) of the 36 subjects tested after treatment. In addition, no subject developed antibodies to efalizumab.

**EFALIZUMAB INCREASES CIRCULATING LYMPHOCYTES**

During efalizumab treatment, an increase in the number of circulating lymphocytes was evident in categories 2 and 3 but not category 1 subjects (Figure 6). The average number of circulating lymphocytes increased by day 7 and remained elevated over pretreatment levels by about 50% in category 2 and about 100% in category 3 for the duration of treatment. Lymphocyte numbers returned to pretreatment levels after the efalizumab was no longer in the plasma. Sustained increases in circulating lymphocyte numbers occurred only at efalizumab dose levels sufficient to maintain sustained decreases in CD11a availability. Absolute neutrophil counts were unchanged.

**COMMENT**

The overall correlation between the effects of different dose levels on CD11a availability and histologic or clinical outcomes supports the purported mechanism that the therapeutic action of efalizumab is linked to its effects on CD11a. In this study, 0.1-mg/kg doses of efalizumab (category 1) failed to maintain saturation or down-modulation of CD11a on circulating T cells. At doses of 0.3 mg/kg weekly (category 2), efalizumab was observed to maintain down-modulation of CD11a but did not maintain complete saturation of CD11a binding sites on circulating or plaque T cells. From preclinical in vitro binding data, CD11a binding saturation of more...
than 99% requires a drug concentration of about 5 µg/mL. In the present study, doses of 0.3 mg/kg weekly maintained trough levels of 0.5 µg/mL or less between doses. Not unexpectedly, binding site data for this dose group show incomplete saturation of CD11a. In the higher-dose groups (≥0.3 mg/kg weekly; category 3), mean drug trough levels were 4 to 5 µg/mL between doses. This level is much closer to the in vitro saturation level and was sufficient to down-regulate and saturate CD11a on circulating and cutaneous T cells for a sustained period. The clinical, histologic, and pharmacodynamic effects observed in this study indicate that by reducing the availability of CD11a on circulating and cutaneous T cells, efalizumab can attenuate the inflammatory process and pathologic epidermal hyperplasia that are the hallmarks of psoriasis.

Administration of efalizumab does not result in a decrease in the number of circulating lymphocytes. Rather, it is associated with a 2-fold increase that persisted as long as efalizumab was detectable in the blood. Leukocyte function–associated antigen 1 is an important adhesion molecule in normal lymphocyte trafficking. The increase in circulating lymphocytes may reflect decreased T-cell emigration into skin, demargination, or release from lymph nodes or skin, as a result of CD11a blockade.

Other highly specific immunosuppressive therapies have been used in recent studies. CTLA4Ig is a fusion protein that binds to B7-1 and B7-2 molecules on the surface of antigen-presenting cells and inhibits the CD28/B7-mediated costimulatory signal for T-cell activation. Abrams et al reported that administration of CTLA4Ig improved psoriatic disease activity as measured by the Physician’s Global Assessment and improved histologic variables such as CD3+ T-cell infiltration, K16 expression, and epidermal thickening. More recently, single-dose intravenous infusions of an anti–CD80 (B7-1) monoclonal antibody showed clinical and histologic activity in moderate-to-severe psoriasis. LFA-3-TIP is a fusion protein that binds to CD2 on T cells and inhibits the CD2/LFA-3–mediated costimulatory signal for T-cell activation. Phase 2 studies with LFA3-TIP in moderate-to-severe psoriasis demonstrated clinical efficacy but, in contrast to efalizumab, which does not deplete lymphocytes, LFA3-TIP depleted memory T cells. The mechanism of action may differ among CTLA4Ig, anti-CD80, LFA3-TIP, and efalizumab. Although all of these targeted immunologic therapies are thought to interfere with activation of T cells, efalizumab has the additional potential of interfering with T-cell extravasation into skin.

With doses of 0.1 mg/kg, adverse events were infrequent. At doses of 0.3 mg/kg or greater, most adverse events noted in this study occurred with the initial dose of efalizumab. The incidence of adverse events subsided with subsequent doses, even when the amount of drug given was increased. This finding suggests that continued exposure to efalizumab at levels high enough to maintain CD11a down-modulation induced a conditioned state for adverse events and is consistent with the disappearance of symptoms in subjects who maintained high blood levels of efalizumab.

Overall, these results indicate that substantial disease improvement resulted with administration of multiple doses of efalizumab in doses of at least 0.3 mg/kg weekly, with tolerable adverse effects. This improvement was associated with down-modulation of CD11a on circulating and plaque T cells, decreased numbers of epidermal CD3+ T cells, and decreased keratinocyte ICAM-1 and K16 expression.

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**REFERENCES**


Congratulations to the winner of our February quiz, Eloy Rodrı´guez Dı´az, MD, PhD, Dermatology, Hospital de Cabueñes, Gijon, Spain. The correct answer to our February challenge was necrotic migratory erythema (pseudoglucagonoma syndrome). For a complete discussion of this case, see the OffCenter Fold section in the March Archives (Park YM, Ham SH, Cho SH, Cho BK. Recurrent Annular Erythematous Scaly Patches. Arch Dermatol. 2002;138:405-410).

Be sure to visit the Archives of Dermatology World Wide Web site (http://www.archdermatol.com) to try your hand at the Interactive Quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month’s print edition of the ARCHIVES. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also receive a free copy of the The Art of JAMA II.