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Therapeutics

Anti-E-selectin is ineffective in the treatment of psoriasis: a randomized trial

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Summary

Background Skin-homing, memory T lymphocytes play an important role in the pathogenesis of psoriasis by interacting with the vascular addressin, E-selectin and trafficking into lesional skin. Thus an attractive option for targeted therapy of the disease would be blockade of skin-homing T cells with an antibody directed at E-selectin.

Objective We performed a multicentre, randomized, placebo-controlled trial to investigate the clinical efficacy and side-effect profile of a humanized monoclonal antibody to E-selectin, CDP850, in the treatment of moderate to severe chronic plaque psoriasis.

Methods Patients with moderate/severe chronic plaque psoriasis were selected for study. Nine male subjects (mean age 37 years, range 25–47) were given 20 mg kg^{-1} CDP850 intravenously as a single dose and four subjects (three males, one female; mean age 40 years, range 23–50) received placebo infusion. Clinical response to treatment was assessed using the psoriasis area and severity index (PASI). Skin biopsies were taken for immunohistochemical analysis at the baseline, pre-treatment, visit and also at day 2 and weeks 1 and 4 postinfusion.

Results The treatment was well-tolerated with a minimal side-effect profile. Plasma E-selectin levels were significantly decreased in those subjects who received CDP850 compared with those who had placebo for the entire study period. At the end of study (8 weeks postinfusion), there was no significant reduction in PASI from baseline for either the CDP850 or placebo-treated groups. Immunohistochemical analysis of biopsies taken from lesional psoriatic skin showed that 2 days after dosing with CDP850, staining for E-selectin was decreased, although not absent, on dermal vascular endothelial cells when compared with baseline ($P < 0{\cdot}01$). This decrease in E-selectin expression was maintained 4 weeks after infusion ($P < 0{\cdot}05$). It was not, however, accompanied by a significant reduction in numbers of neutrophils or lymphocytes in the dermis. There was a statistically significant increase in CD1a-positive epidermal Langerhans cells compared with pre-dose levels at week 1 ($P < 0{\cdot}05$).

Conclusions This clinicopathological study shows that anti-E-selectin (CDP850), although a well-tolerated, logical and safe therapy, does not appear to possess a therapeutic role in the treatment of chronic plaque psoriasis.

Key words: cutaneous lymphocyte associated antigen, E-selectin, memory T cells, psoriasis

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E-selectin, previously known as endothelial leucocyte adhesion molecule-1, is a single chain glycoprotein of molecular mass 115 kDa. It belongs to a family of adhesion molecules that contain lectin, epidermal growth factor (EGF)-like and complement binding-like domains.[1] E-selectin mediates neutrophil, monocyte and eosinophil adhesion to activated vascular endothelium via carbohydrate ligands such as sialyl-Lewis X.[2] Furthermore, there is now considerable evidence to suggest that skin-homing, memory T lymphocytes, important in the pathogenesis of psoriasis,[3] traffic into lesional skin via interaction between a molecule structurally related to sialyl Lewis X, namely cutaneous lymphocyte associated antigen (CLA), and its vascular addressin, E-selectin.[4–7] Furthermore, E-selectin appears to recruit T-h1 T cells specifically, the predominant T-cell subtype present in psoriasis.[3,8]

Although E-selectin is expressed only faintly on upper dermal blood vessels in normal skin, it is markedly upregulated by pro-inflammatory cytokines, including interleukin-1 and tumour necrosis factor α.[9] Psoriatic plaques are characterized by strong expression of E-selectin on the luminal surface of capillary and postcapillary endothelial cells.[10–12] Interestingly, E-selectin is not expressed in the synovium of joints affected by psoriatic arthritis.[13] In contrast to *in vitro* observations that show E-selectin expression to be transient, even in the presence of continued cytokine stimulation,[1,2] upregulation of E-selectin in psoriatic skin is sustained.[11] As expression of E-selectin is minimal on vascular endothelial cells in normal skin, an anti-E-selectin antibody should theoretically show little reactivity with the vasculature of uninflamed tissues. This feature of specificity, together with the recent molecular engineering of an adhesion-blocking, humanized antibody with minimal effector functions (CDP850 previously designated SPLAT-1),[14,15] suggests that such an antibody should be safe to administer to patients with psoriasis and may represent a highly specific form of immunomodulatory therapy. We thus performed a double-blind, placebo-controlled clinical study to investigate the safety profile and efficacy of CDP850 in the treatment of chronic plaque psoriasis. Furthermore, we performed a concomitant immunohistological study to determine whether CDP850 inhibited E-selectin expression by dermal endothelium and the inflammatory infiltrate in psoriasis plaques.

Methods

Patients

A double-blind, randomized, placebo-controlled trial to investigate the efficacy, side-effect profile and patient tolerability of anti-E-selectin (CDP850) in the treatment of moderate to severe chronic plaque psoriasis was conducted at six dermatology centres in the United Kingdom. Patients of either sex, aged 18–70 years, with moderate or severe chronic plaque psoriasis of psoriasis area and severity index (PASI)[16] ≥ 12, were recruited. Patients with impaired renal or hepatic function, or with significant systemic disease were excluded. None of the patients were receiving either systemic or phototherapy. All topical therapies, apart from emollients, were discontinued 2 weeks prior to entry into the study. Thirteen patients (12 males, one female, mean age 39 years) were enrolled into this study.

Study design

The study protocol was approved by the local research ethics committees for each centre. Written informed consent was obtained from each subject prior to entry into the study. Subjects were randomly assigned to a single intravenous dose of either CDP850 (Celltech R&D Ltd, Slough, Berkshire, U.K.) or placebo treatment in a ratio of 2 : 1 on the basis of a computer-generated randomization code. Patients, study coordinator and study physician were unaware as to which group each patient had been assigned. The dosage of CDP850 used in this study had been elucidated from a previous open pharmacokinetic study in patients with psoriasis (Dr M.Sopwith, personal communication). This showed that 20 mg kg^{-1} of CDP850 was not only well tolerated but also reduced circulating E-selectin levels below the limit of assay detection (1 ng mL^{-1}) for several weeks postinfusion (data not shown). Patients were assessed by the same physician at screening, 24 h prior to infusion and at 1, 2, 4 and 8 weeks after administration of CDP850. Photographs of a previously identified, untreated and photoprotected target plaque of psoriasis were taken at the preinfusion visit in all subjects and also post-treatment in any in whom a significant clinical response was observed. The treatment code was not broken until the final patient had completed the study protocol.

Efficacy assessments

PASI was the principal outcome measure used to evaluate the efficacy of CDP850; this measure of severity of psoriasis ranges from 0 = no disease to 72 = most severe psoriasis.[16] In addition, the overall therapeutic response was assessed subjectively by the physician (4 = cleared, 3 = marked improvement, 2 = improvement, 1 = slight improvement, 0 = unchanged, −1 = slightly worse, −2 = moderately worse or −3 = mark-markedly worse as compared with the preinfusion clinical status). Subjects were classed as 'responders' if they had a decrease in PASI of more than 75% as compared with preinfusion values and/or exhibited a marked response or clearance of their disease.

Immunohistochemistry

Single 4-mm punch biopsies were taken under local anaesthesia (1% lidocaine with adrenaline) from the active edge of the previously identified target plaque of psoriasis at baseline as well as at day 2, week 1 and week 4 postinfusion. These specimens were bisected, half processed to formalin for conventional histological examination and the other half embedded in optimal cutting temperature embedding medium compound (OCT, Miles Laboratories, Elkhart, IN, U.S.A.), frozen in melting isopentane and stored in liquid nitrogen until required. Cryostat sections of 5 μm thickness were air dried for 15 min, fixed in acetone at 4 °C for 10 min, washed and non-specific binding blocked with 20% normal swine serum. The primary antibody panel used in this study is provided in Table 1. Primary antibody binding was detected using a conventional peroxidase-antiperoxidase reaction and visualized using 3,3′-diaminobenzidine as chromogen. All secondary reagents were obtained from Dako Ltd (High Wycombe, Buckinghamshire, U.K.). Sections were counterstained with Mayer's haematoxylin, dehydrated through graded alcohols, cleared and mounted. Controls included omission of the primary antibody and substitution of the primary antibody by one of the same class but of irrelevant specificity. All slides were scored according to a previously described semiquantitative assessment of staining by a single-blinded observer (J.N.W.N.B.).

Safety assessments

All adverse events, subjective or objective, were recorded by the study physician. As well as a standard physical examination and record of vital signs, a haematological and blood chemistry profile was performed at each visit (pre-dose, days 1 and 2, weeks 1, 2, 4 and 8 postinfusion). During the infusion, and for 24 h afterwards, the patients were closely monitored on a medical unit and 4-hourly measurements of temperature, pulse, blood pressure and respiratory rate recorded.

Statistical methods

Non-parametric statistical analyses (Mann–Whitney *U*-test) were used in the clinical part of the study. Two-tailed tests were used throughout. Values are expressed as mean ± SD. A statistical level of significance was defined as the 5% level for clinical and immunohistochemical measurements using the Wilcoxon signed rank sum test. Data analysis was performed using the SPSS software package (SPSS version 7·5.1, SPSS Inc, Chicago, IL, U.S.A.).

Results

Thirteen patients (12 males, one female; mean age 39 years (range 23–50 years) with untreated, stable

Table 1. Panel of antibodies used for immunohistochemical analysis

Antibody	Specificity	Dilution	Source
Leu 3a	CD4	1 : 10	Becton Dickinson, Oxford, U.K.
Leu 2a	CD8	1 : 10	Becton Dickinson
HECA-452[6]	CLA	1 : 10	Celltech R&D Ltd, Slough, Berkshire, U.K.
NP57	Neutrophil elastase	1 : 100	Dako, High Wycombe, Buckinghamshire, U.K.
EMB11	CD68	1 : 100	Dako
1.2B6[29]	E-selectin	1 : 50	Celltech R&D Ltd
ENA-2[a17]	E-selectin	1 : 50	Celltech R&D Ltd
Ki-67	MIB-1	1 : 20	Immunotech SA, Marseilles, France
JC70A	CD34	1 : 50	Dako
Leu 6a	CD1a	1 : 25	Becton Dickinson
EN4	Human endothelium	1 : 100	Monosan Sanbiobir, Uden, the Netherlands

[a] The parent antibody of CDP850; this binds to the same epitope as CDP850.

chronic plaque psoriasis were enrolled into this double-blind, randomized, placebo-controlled study. Nine subjects (all male, mean age 37 years, range 25–47 years, duration of disease 18·5 ± 13·7 years; mean baseline PASI 17·9 ± 4·9) received 20 mg kg^{-1} CDP850 intravenously as a single infusion over 4–6 h. Four subjects (three males, one female, mean age 40 years, range 2–50 years, duration of disease 14·6 ± 3·2 years; mean baseline PASI 20·3 ± 8·0) received the placebo infusion.

Clinical response to treatment as assessed by psoriasis area and severity index and overall response

At the end of study (8 weeks postinfusion), the mean PASI for the CDP850-treated group was 16·4 ± 9·7 and for the placebo group 17·3 ± 8·0 (statistically not significant from baseline; Fig. 1). There was no statistical difference in PASI between the two groups at any assessment point in the study. No individual subject, whether having received CDP850 or placebo therapy, could be classified as a 'responder'.

Side-effect profile

There were no haematological or biochemical abnormalities detected in any of the patients prior to or throughout the study period. No clinically significant side-effects considered to be due to CDP850, were reported. Two patients, both treated with CDP850 received rescue inpatient topical medication at 8 days and 19 days after infusion, respectively, due to worsening of their psoriasis and were excluded from the trial. Both patients were included in the statistical analysis for the study.

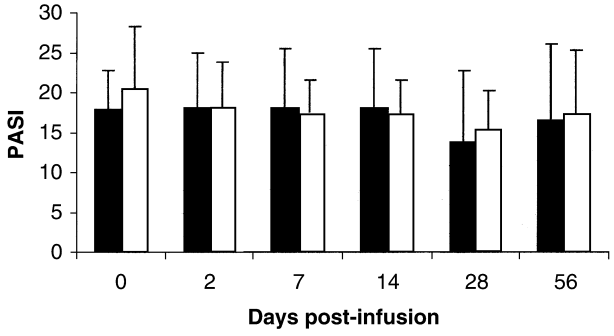

Figure 1. Clinical response of psoriasis, as assessed by psoriasis area and severity index (PASI), to anti-E-selectin (CDP850) and placebo infusion. There was no statistical difference in PASI between the two groups, at any assessment point in the study. ■ CDP850, $n = 9$; □ placebo, $n = 4$. Values are mean ± SD.

Pharmacokinetics

In all nine patients receiving active treatment, plasma levels of CDP850 remained elevated after the infusion. Mean CDP850 concentration (with 95% confidence intervals) at 1 week postinfusion was 199 μg mL^{-1} (172–231), at 4 weeks 102 μg mL^{-1} (78–136) and at week 8, 35 μg mL^{-1} (26–47). Only a very low and transient humoral immune response to CDP850 was detected at weeks 1, 4 and 8 postinfusion (data not shown). In addition, E-selectin levels stayed below the level of detection of the assay for this time period (data not shown).

Immunohistochemistry

No effect was noted on 1.2B6 expression (which reflects total E-selectin levels on endothelial cells) in lesional skin at day 2, week 1 and week 4 postinfusion (Fig. 2a,b). Two days after dosing, however, it was noted that staining with ENA-2, which binds to the same epitope on E-selectin as does CDP850, was decreased, although not absent, on papillary dermal endothelial cells ($P < 0·01$; Fig. 3a,b). This staining pattern was maintained at 4 weeks postinfusion ($P < 0·05$). No concomitant decrease in T-lymphocyte or neutrophil infiltration was observed. Double-labelling experiments were not performed, and thus it was not possible to assess accurately the proportion of lymphocytes expressing CLA. There was, however, a statistically significant increase in CD1a-positive epidermal Langerhans cells at week 1 postinfusion compared with pre-dose baseline levels ($P < 0·05$; Fig. 4a,b). No such increase in epidermal Langerhans cells was observed in the biopsies taken from subjects treated with placebo.

Discussion

This is the first double-blind, placebo-controlled investigation of intravenous anti-E-selectin, CDP850, in the treatment of moderate to severe chronic plaque psoriasis. Previous studies, in animal models, have shown that monoclonal antibodies to E-selectin can block the recruitment of neutrophils and lymphocytes into sites of cutaneous inflammation. Using recombinant DNA techniques, a humanized monoclonal antibody (CDP850, previously known as SPLAT-1), has been developed and found to possess a long circulating half-life (greater than 14 days in humans) coupled with low immunogenicity.[14,15] CDP850 binds an epitope in the

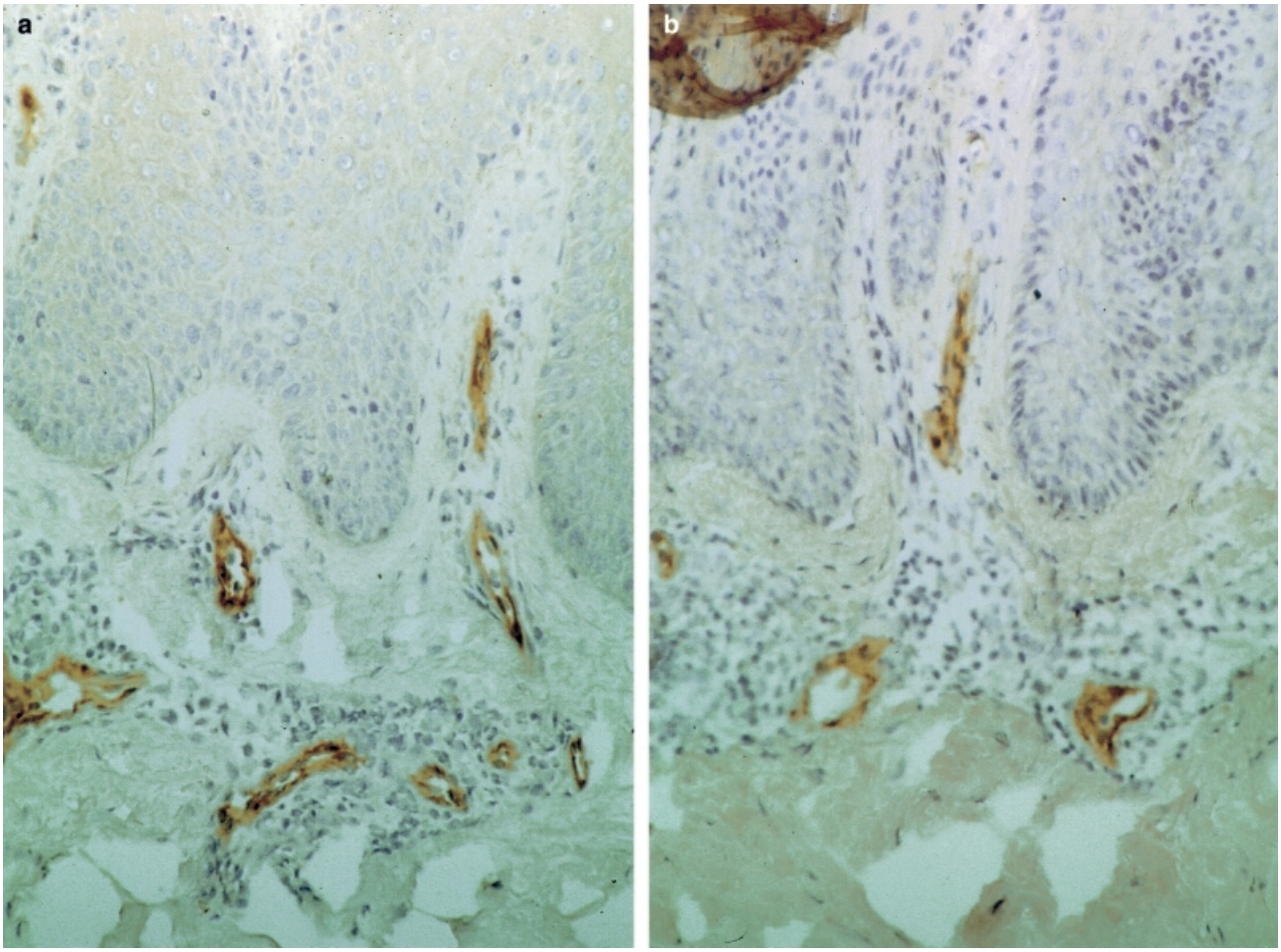

Figure 2. Photomicrograph of lesional psoriatic skin stained with monoclonal antibody 1.2B6: (a) pretreatment; (b) 2 days after intravenous administration of anti-E-selectin, CDP850 (original magnification ×25). Endothelium stained brown. There is no decrease in 1.2B6 staining following CDP850 infusion.

lectin/EGF region of E-selectin and potently blocks the binding of CLA-positive human lymphocytes to E-selectin-expressing cells *in vitro*. It also inhibits the tumour necrosis factor-α-mediated trafficking of leucocytes into human skin grafted on to SCID mice.[15] However, despite the theoretical potential of E-selectin blockade as a selective and effective therapy for psoriasis, the results from our trial indicate that administration of CDP850, perhaps surprisingly, possesses little beneficial clinical efficacy in this condition.

CDP850 was found to be present in substantial amounts in the peripheral blood of all patients on active therapy for up to 8 weeks postinfusion. Prolonged binding to and clearance of circulating E-selectin by CDP850 at doses between 0·3 and 20 mg kg^{-1} was also observed both in this and a previous pharmacokinetic study (data not shown). The observation that staining with the antibody ENA-2, which binds to the same epitope on E-selectin as CDP850,[17] was decreased on papillary dermal endothelial cells following infusion of CDP850 suggests competitive binding and blockade of this epitope by CDP850. It is known that the prolonged expression of E-selectin by microvascular endothelial cells is at least in part due to endocytosis and degradation of the protein.[18,19] The residual ENA-2 staining observed in our study may thus represent intracellular E-selectin that is irrelevant to leucocyte trafficking and/or lymphocyte/neutrophil accumulation. This intracellular pool of E-selectin could not be bound by circulating CDP850 *in vivo* but may have been available for interaction with ENA-2 antibody during the processing of tissue prior to immunohistochemical analysis.

It is possible that the absence of a measurable clinical difference between the anti-E-selectin and placebo-treated groups is because CDP850 may better be able to

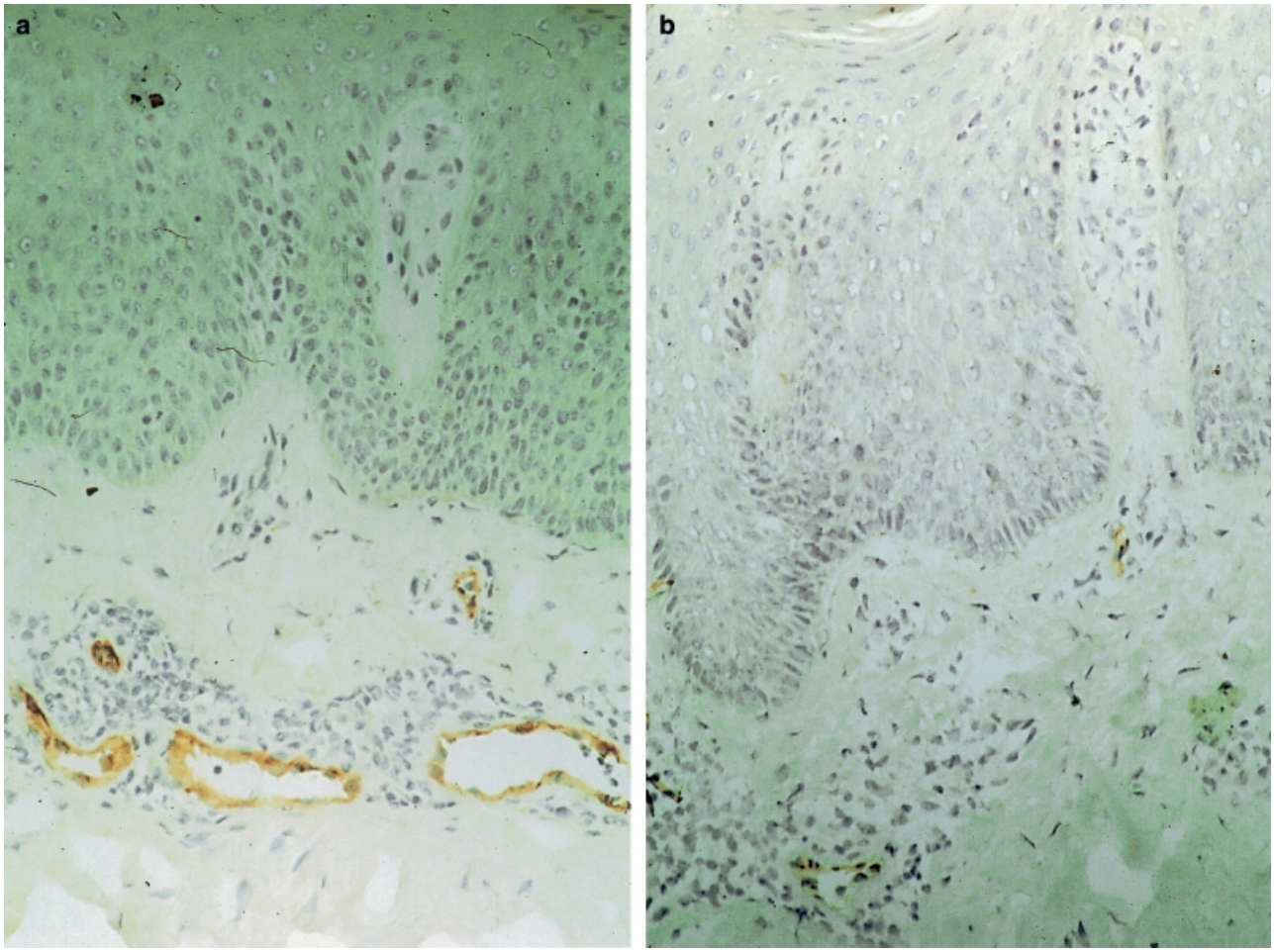

Figure 3. Photomicrograph of lesional psoriatic skin stained with monoclonal antibody ENA-2: (a) pretreatment; (b) 2 days after intravenous administration of anti-E-selectin, CDP850 (original magnification ×25). Endothelium stained brown. Note reduction in ENA-2 staining following CDP850 infusion.

prevent relapse once clearance of psoriasis has been achieved with other therapies such as cyclosporin. Furthermore, a dose of 20 mg kg^{-1} CDP850 is perhaps too low for efficacy but previous pharmacokinetic studies indicate that this dose is sufficient significantly to lower circulating levels of E-selectin for a prolonged period. Alternative explanations for CDP850's lack of therapeutic effect in our patients with psoriasis might also include poor binding to human E-selectin or decreased ability to inhibit its function *in vivo*. Furthermore, recently discovered T-cell epitopes for E-selectin that are distinct from sialyl Lewis X residues may be of importance in the psoriatic process but not affected by CDP850 blockade.[20] In a similar fashion, alternative pathways for leucocyte adherence to endothelium (intercellular adhesion molecule-1, P-selectin and CD11/CD18 complex)[21] may not be affected by anti-E-selectin treatment.

The increase in epidermal Langerhans cells in psoriasis plaques following administration of CDP850 merits further study. Langerhans cells represent a subset of bone marrow-derived dendritic cells, which, after capturing foreign antigen, migrate from the epidermis, enter local lymph nodes and present these peptide fragments to naive T cells.[22] Previous work has shown that the number of epidermal Langerhans cells in chronic plaques of psoriasis is decreased,[23] although the underlying reason for this is still unclear. The increase in Langerhans cells within psoriatic epidermis after treatment with anti-E-selectin is of interest, particularly as similar increases in Langerhans cell frequency have been observed with other, clinically successful treatments for psoriasis such as tacrolimus and systemic retinoids.[24,25] As Langerhans cells are known to express the E-selectin ligand sialyl Lewis X[26,27] we speculate that CDP850 may have inhibitory

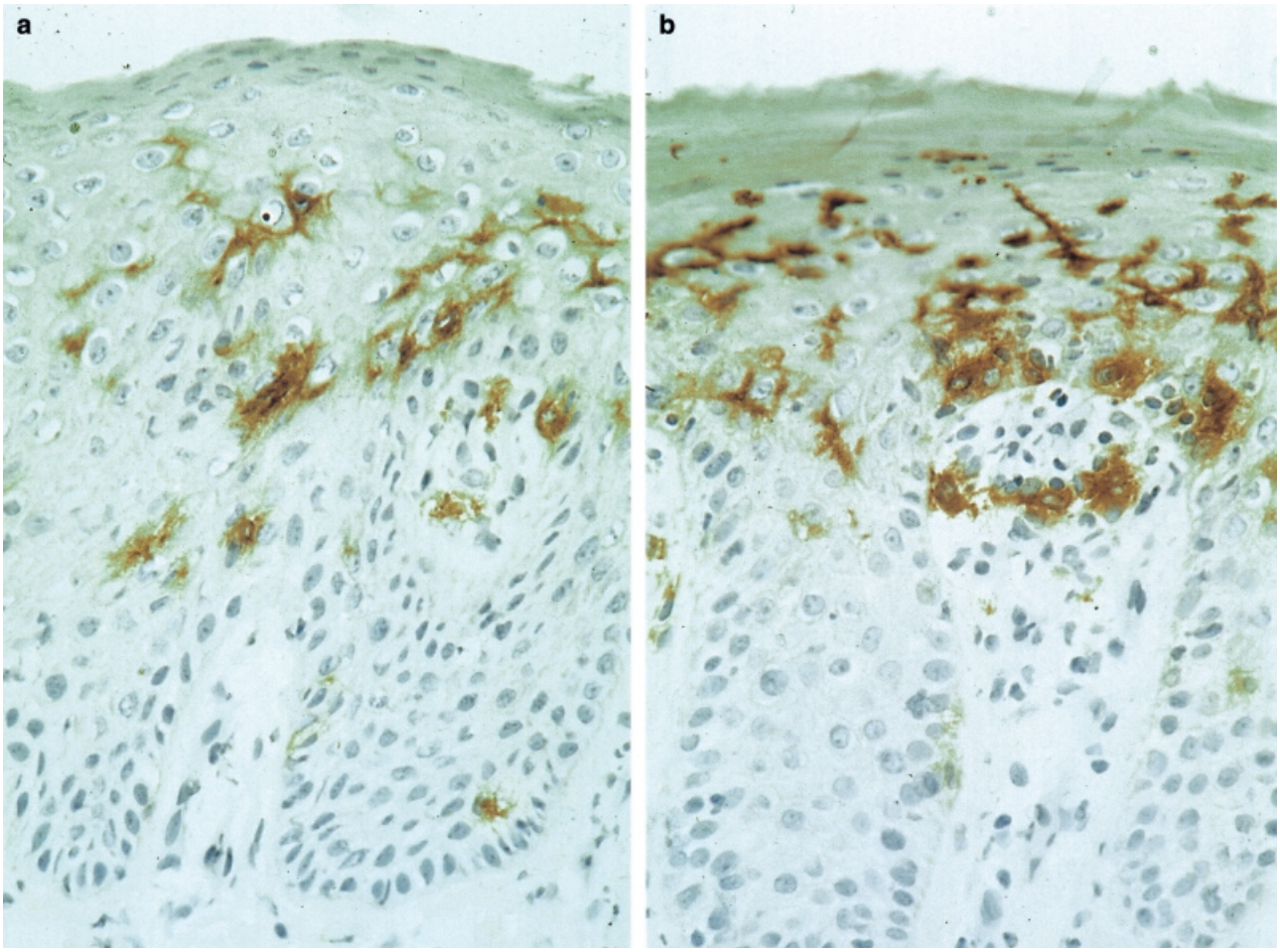

Figure 4. Photomicrograph of lesional psoriatic skin stained with monoclonal antibody CD1a: (a) pretreatment; (b) 1 week after intravenous administration of anti-E-selectin, CDP850 (original magnification ×40). Langerhans cells stained brown. There is an increase in the number of Langerhans cells following CDP850 infusion.

effects on Langerhans cell migration between the epidermis and afferent lymphatics. This idea at present must remain speculative as adhesion events on lymphatic endothelium have not been clearly defined. By contrast the entry of dendritic cells into the skin via vascular endothelium has been shown to be dependent on E-selectin.[28]

The pathomechanisms for leucocyte trafficking in psoriasis, and the involvement of E-selectin, are well established. Blockade of E-selectin would appear to represent a novel and selective therapeutic strategy for this condition. However, the findings from our study conclude that treatment with CDP850, a humanized antibody against E-selectin, at a single dose of 20 mg kg^{-1}, although well tolerated and safe, does not appear to possess a therapeutic role in the treatment of moderate to severe chronic plaque psoriasis. This may indicate that other adhesion molecule-mediated events are more important for the binding of leucocytes to dermal endothelium and subsequent egress into the dermis and epidermis in psoriasis.

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