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HOT CLINICAL STUDY

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Pan-selectin antagonism improves psoriasis manifestation in mice and man

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Abstract The selectin family of vascular cell adhesion molecules is comprised of structurally related carbohydrate binding proteins, which mediate the initial rolling of leukocytes on the activated vascular endothelium. Because this process is one of the crucial events in initiating and maintaining inflammation, selectins are proposed to be an attractive target for the development of new antiinflammatory therapeutics. Here, we demonstrate that the synthetic pan-selectin antagonist bimosiamose is effective in pre-clinical models of psoriasis as well as in psoriatic patients. In vitro bimosiamose proved to be inhibitory to E- or P-selectin dependent lymphocyte adhesion under flow conditions. Using xenogeneic transplantation models, bimosiamose reduced disease severity as well as development of psoriatic plaques in symptomless psoriatic skin. The administration of bimosiamose in patients suffering from psoriasis resulted in a reduction of epidermal thickness and lymphocyte infiltration. The clinical improvement was statistically significant ($P = 0.02$) as analyzed by comparison of psoriasis area and severity index before and after treatment. Assessment of safety parameters showed no abnormal findings. These data suggest that pan-selectin antagonism may be a promising strategy for the treatment of psoriasis and other inflammatory diseases.

Keywords Antagonists · Inflammation · Psoriasis · Selectins

Abbreviations SCID: Severe combined immunodeficiency

Introduction

Chronic inflammatory disorders cover a heterogeneous group of diseases including asthma, rheumatoid arthritis and psoriasis. Despite their clinical heterogeneity, these diseases have one mechanism in common, infiltration of leukocytes from the circulation into the surrounding tissue of the affected organ (transmigration) (Ley 1996; Springer 1994).

Transmigration is a complex cascade of molecular events initiated by tethering and rolling of leukocytes to activated endothelium. This process is considered to be the primary event in the response to inflammatory stimuli. It is mediated by the selectin family of vascular adhesion molecules which is comprised of three structurally related calcium-dependent carbohydrate binding proteins, E-, P- and L-selectin. While L-selectin is expressed on the surface of leukocytes, surface expression of endothelial E- and P-selectin is upregulated during inflammation (Kansas 1996).

Based on their key role in mediating leukocyte transmigration, selectins constitute an attractive target for therapeutic intervention. However, there is functional redundancy between E- and P-selectin (Tietz et al.

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1998). Thus, simultaneous blocking of E- and P-selectin on endothelial cells proved to be more efficacious than blocking of either E- or P-selectin alone (Issekutz and Issekutz 2002). In addition, blockage of L-selectin on leukocytes has been shown to be effective in preventing leukocyte transmigration (Watson et al. 1991). Consequently, targeting all three selectins (pan-selectin antagonism) is considered to be a therapeutic strategy for inflammatory disorders (Sperandio et al. 2004).

In this study, we explored the therapeutic potential of pan-selectin antagonism in psoriasis. In this disease, an association between infiltration of activated leukocytes into the skin, proliferation of resident T-cells as well as marked elevation of tissue expression of adhesion molecules, particularly E- and P-selectin, has been demonstrated (Terajima et al. 1998; Chu et al. 1999; Boyman et al. 2004). In humans, targeting only a single selectin, e.g., E-selectin, was not effective in modulating disease activity of psoriasis (Bhushan et al. 2002). By applying the pan-selectin antagonist bimosiamose (Kogan et al. 1998) in preclinical and clinical models of psoriasis, we demonstrated efficacy in both, suggesting that pan-selectin antagonism may be a valuable therapeutic strategy for inflammatory disorders.

Material and methods

Chemicals and cell lines

Bimosiamose is the name for 1,6-*Bis* [3-(3-carboxymethylphenyl)-4-(2-α-D-mannopyranosyloxy)-phenyl]hexane C46H54O16 (Kogan et al. 1998). For all experiments and studies, a sterile 0.08% citrate buffered 0.9% NaCl solution (placebo) containing 100 mg/ml bimosiamose was used. HL-60 and Jurkat cells were obtained from DSMZ (Braunschweig, Germany) and cultured in RPMI 1640 supplemented with 10% fetal calf serum, 2 mM L-glutamine and 100 U/ml pencillin/streptomycin (all from Biochrom, Berlin, Germany). For activation, Jurkat cells were cultured in the presence of 10 nM phorbol myristate acetate (PMA)(Sigma, Deisenhofen, Germany) for 2 days.

Flow chamber assay

Cell attachment under flow conditions was determined using a parallel flow chamber according to the manufacturer's protocol (Glycotech, Gaithersburg, MD, USA). Briefly, polystyrene culture dishes (Corning, Wiesbaden, Germany) were coated with E- or P-selectin/Fc chimera (R&D Systems, Wiesbaden, Germany) or human immunoglobulin G (Dianova, Hamburg, Germany) and subsequently blocked with bovine serum albumin (Sigma, Deisenhofen, Germany). The dishes were fitted into the parallel flow chamber and mounted onto an inverted phase-contrast microscope (Olympus, Hamburg, Germany) equipped with a CCD camera (JVC) connected to a personal computer. Employing a peristaltic pump (Ismatec, Wertheim-Mondfeld, Germany), flow chamber experiments were performed in a recirculating configuration (without any visible pulsation) with a final concentration of 2.4 million cells/ml. The number of cells that attached to the substrate 5 min after continuous flow at a calculated flow shear of 1 dyne/cm^2 was counted from 5 low power fields. The calculated mean was expressed as cells/field.

SCID mouse models of psoriasis

The applied procedures for human skin/SCID mouse chimera and tissue processing, activation of autologous immunocytes, clinical assessment and light microscopic evaluation have been described previously (Dam et al. 1998) except for the following modifications: PP-model: Animals transplanted with psoriatic plaque were randomized to intradermal administration of either bimosiamose 200 mg/kg or phosphate buffered saline (PBS). PN-model: Prepared autologous immunocytes were reincubated with bimosiamose (200 μg/ml) or diluent control (PBS).

This study was approved by the University of Michigan Human Subjects Committee (Ann Arbor, MI, USA), and informed consent was obtained from each patient before the procedure.

Patients

A protocol outlining the use of bimosiamose in patients with moderate to severe psoriasis was approved by the Institutional Review Board of the Medical Faculty of the Charite, and written informed consent was obtained from all patients. Before enrolment on study, systemic therapies were discontinued for at least 3 months; phototherapy was not administered for at least 2 months; and topical treatments other than emollients were not administered for two or more weeks. Five patients with chronic plaque psoriasis (age: 29–59 years, two females and three males) were chosen.

Study design and treatment

The study was designed as an open-label, observational pilot study. Patients received subcutaneous intralesional administration of bimosiamose over a period of 14 days at a daily dosage of 600 mg/day. Patients were examined daily during the treatment phase. Safety was monitored on the basis of physical examination, vital signs, assessment for infections and clinical laboratory analyses. Primary efficacy was assessed before and at the end of the therapy in the psoriasis area and severity index (PASI) (Fredriksson and Pettersson 1978) calculated.

Biopsies for measurements of epidermal thickness and CD3 mRNA were obtained before (day 0) and after treatment (day 14) from the same psoriatic plaque which bimosiamose was applied.

Skin lesion assesment

The target skin lesion and control skin lesion assessment was performed for the symptoms erythema (E), induration (I), and desquamation (D), with sum scores recorded for each of these symptoms. The target lesion for injection was greater than 2 cm^2 in area, and preferably not sun exposed. A second afflicted but non-injected psoriatic area of approximately the same size and condition served as control (control skin lesion). The parameters E, I, and D were graded in half-point increments according to the following scale: 0 = none (for E, postinflammatory hyperpigmentation was graded as 0) 1 = slight, 2 = moderate, 3 = marked and 4 = very marked.

Analysis of plasma levels of bimosiamose

Prior to initiation of therapy and at 1, 2, 4, and 6 h after injection on day 1 and 14, and pre-dose only from days 2 to 13, plasma bimosiamose levels were measured by liquid chromatography-mass spectrometry (Finnigan MAT TSQ 7000 mass spectrometer; Column: YMC-Pack Phenyl, 150 mm×21 mm ID, S-5 µm, 120Å; Guard Column: YMC-Pack Phenyl, 10 mm×4.6 mm, Mobile phase: Formic acid [0.1%]: acetonitril [60/40, v/v] as described elsewhere (internal report: Bruce J, Kyle J, Barkby C, Mc Guire G: Determination of concentrations of bimosiamose in human plasma samples following intradermal administration of bimosiamose disodium. Inveresk Research 2002.).

Molecular biological analyses

For molecular biological analyses, the skin biopsies were obtained before bimosiamose therapy (day 0) and at day 14 (end of therapy). For isolation of total RNA from human skin biopsies, samples snap frozen in Invisorb® lysing solution (Invitek, Berlin, Germany) were homogenized during thawing by means of Ultraturrax tissue homogenizer (Jahnke and Kunkel, Staufen, Germany). Isolation of total cellular RNA was done by use of Invisorb® RNA kit II (Invitek). mRNA was reverse transcribed and analyzed by TaqMan® PCR using the ABI Prism® 7700 Sequence Detection System (Applied Biosystems, Weiterstadt, Germany) as described previously (Wolk et al. 2002). For detection of human CD3 and house-keeping gene hypoxanthine phosphoribosyl-transferase 1 (HPRT), we established detection systems with amplification efficiencies of 100% using exon–exon boundaries spanning 6-carboxy-fluorescein/6-carboxy-tetramethyl-rhodamine double-labeled probes. Expressions were calculated relative to the data for HPRT obtained with the every matching assay.

Statistical analysis

Statistical significance was assessed by the Student's t test. A probability value of $P < 0.05$ was considered significant.

Results and discussion

In vitro effect of bimosiamose on dynamic cell adhesion

Psoriasis is considered as a lymphocyte mediated inflammatory disease (Assadullah et al. 2001). Therefore, we studied the effect of bimosiamose on the adhesion of human lymphoid Jurkat cells to E- and P-selectin under shear flow conditions. As control, we used promyeloid HL-60 cells for which efficacy of bimosiamose has been demonstrated under static and dynamic conditions (Kogan et al. 1998; Onai et al. 2003).

Using a parallel flow chamber approach, Jurkat cells attached and subsequently rolled on immobilized E- or P-selectin at a shear stress of 1 dyne/cm^2. The presence of bimosiamose at a concentration known to be effective in other in vitro assays reduced this interaction (Fig. 1a).

In psoriasis, lymphocytes leaving the circulation at points of inflammation are activated. We mimicked activation by stimulating Jurkat cells with phorbol ester (PMA) for 2 days prior to flow chamber experiments. PMA treatment of Jurkat cells is known to induce the expression of the early activation marker CD69 (Castellanos Mdel et al. 2002). In addition, PMA increased the prevalence and density of two epitopes on Jurkat cells defined by terminal sialylated, fucosylated *N*-acetyllactosamine structures, HECA 452 and CSLEX1 (Knibbs et al. 1996). Cutaneous lymphocyte antigen (CLA) defined by HECA 452 is suggested to be an E-selectin ligand present on skin-homing lymphocytes (Picker et al. 1990; Berg et al. 1991). In comparison with untreated Jurkat cells our flow chamber experiments with PMA-treated Jurkat cells revealed an increase in adhesion to immobilized E-selectin but not to P-selectin (Fig. 1a). This is in line with the observation that in Jurkat cells PMA-induced gene expression of fucosyltransferase VII (FucT-VII), an enzyme pivotally involved in the post-translational modification of selectin ligands, lead to enhanced rolling on E-selectin (Barry et al. 2003). Accordingly, analysis of PMA-stimulated Jurkat cells confirmed an increase in FucT-VII mRNA and expression of CD69 in our hands (data not shown). Interestingly, activation of Jurkat cells resulted in a higher sensitivity for inhibition of adhesion to E-selectin in the presence of bimosiamose (Fig. 1a). Our data gives first in vitro evidence that bimosiamose is also effective in inhibiting the binding of lymphocytes to P- and E-selectin.

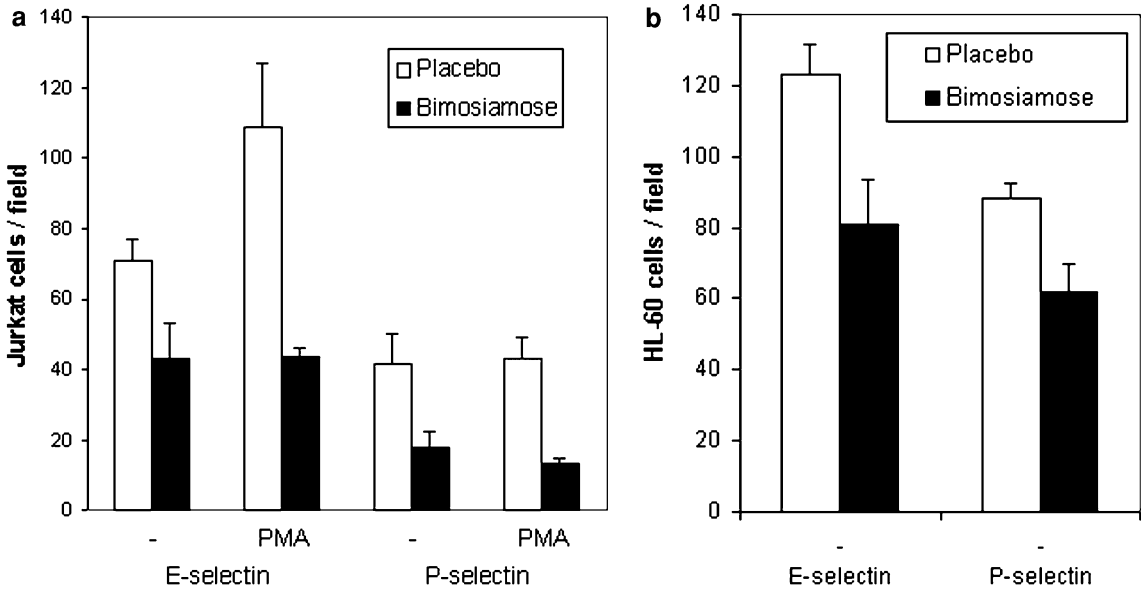

Fig. 1 In vitro effect of bimosiamose on dynamic cell adhesion **a** Jurkat cells cultured with or without PMA were perfused over polystyrene dishes immobilized with E- or P-selectin/Fc chimera (5 μg/ml) in the presence of 129 μM bimosiamose (*filled bars*) or placebo control (*open bars*). As shown by the number of attaching cells/field after 5 min, adhesion to E- or P-selectin under conditions of shear flow was significantly inhibited by bimosiamose ($P < 0.05$). Activation of Jurkat cells by PMA significantly leads to an increase in attachment to E-selectin that was more sensitive to inhibition by bimosiamose compared to inhibition of non-activated cells ($P < 0.05$). **b** HL-60 cells were perfused over petri dishes immobilized with E- or P-selectin/Fc chimera (2–5 and 10 μg/ml, respectively) in the presence of bimosiamose or placebo control. Bimosiamose significantly reduced ($P < 0.05$) attachment of HL-60 cells to E- and P-selectin/Fc chimera. Represented are the mean and standard deviation of five experiments. No attachment was seen when dishes were coated with human IgG (10 μg/ml) or in the presence of 5 mM EDTA (data not shown)

Our control experiments confirmed the ability of bimosiamose to reduce dynamic adhesion of promyeloid HL-60 cells to E- and P-selectin (Fig. 1b).

Bimosiamose is effective in two models of SCID-mouse psoriasis

To investigate bimosiamose in disease models of psoriasis, we employed validated settings where human psoriatic grafts are transplanted on SCID mice (PP-model) or uninvolved skin from psoriatic patients transplanted on SCID mice is subsequently injected with activated autologous immunocytes (PN-model) (Dam et al. 1999; Boehncke et al. 1994).

PP-model

In contrast to control diluent injection (PBS), repeated injections of bimosiamose twice a week for 3 weeks into psoriatic xenotransplants changed the severity of scaliness, induration and erythema as indicated by the semi-quantitative score of psoriasis (Fig. 2). Light microscopic analysis of the correspondent transplant showed in PBS-treated specimens, typical histological changes of psoriasis: hyperkeratosis, parakeratosis, acanthosis with elongated rete ridges, and a dense mononuclear cell infiltrate. In contrast, the histological evaluation of bimosiamose treated grafts showed

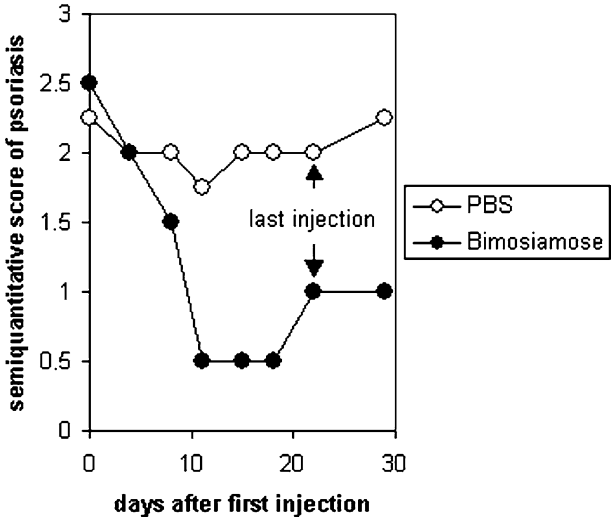

Fig. 2 Effect of bimosiamose in a psoriasis disease model (PP) in SCID mice. Local injections twice a week for three weeks of PBS (*open circle*) or 200 mg/kg bimosiamose (*filled circle*) into xenografts obtained from one psoriatic plaque of one patient. Clinical assessments during the injection and follow-up phase of the study are indicated on a semi-quantitative scale of psoriasis where a maximal score of 3 represents severe scaliness, induration and erythema of the psoriatic xenografts. Compared to PBS injection with bimosiamose reduced the semiquantitative score of psoriasis already 10 days after first treatment. Shown are the means from single xenografts of two mice. A similar kinetic could be reproduced with other transplants of the same patient and with transplants from a different psoriatic donor (data not shown)

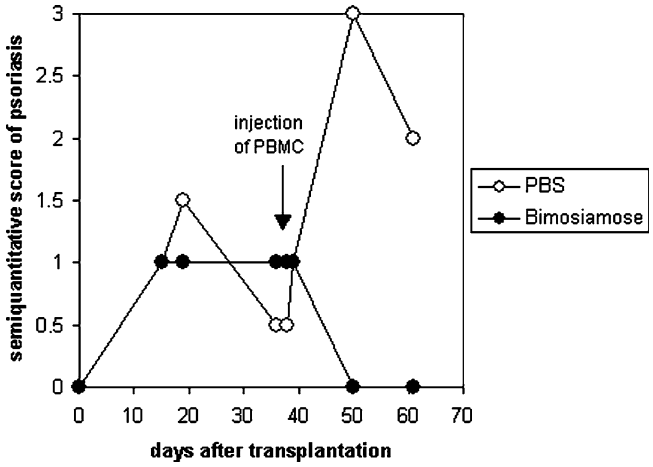

Fig. 3 Effect of bimosiamose on a psoriasis disease model (PN) in SCID mice. Injection of activated autologous PBMC pretreated with PBS (*open circle*) or 200 μg/ml bimosiamose (*filled circle*) into xenografts obtained from uninvolved skin of one psoriatic patient. Clinical assessments during the injection and follow-up phase of the study are indicated on a semi-quantitative scale of psoriasis where a maximal score of 3 represents severe scaliness, induration and erythema of the psoriatic xenografts. Pre-treatment of PBMC with bimosiamose prior to injection resulted in a decrease in the semiquantitative score of psoriasis compared to PBS control. Shown are values from one xenograft of one mouse. Similar endpoints could be reproduced with grafts from another psoriatic donor (data not shown)

reduction in epidermal thickness and cellular infiltrate (data not shown).

PN-model

Uninvolved psoriatic skin was transplanted to SCID mice. Treatment of activated autologous PBMC with PBS prior to injection (day 36 after transplantation) in the xenografts resulted in development of a psoriatic phenotype as indicated by an increased semiquantitative score of psoriasis. In contrast, if autologous PBMC were treated with bimosiamose prior to intradermal injection, the semiquantitative score of psoriasis decreased (Fig. 3).

A recent observation suggested that plaque development in xenotransplantation models of psoriasis is based on expansion of graft resident lymphocytes, rather than by recruitment of circulating cells (Boyman et al. 2004). Consequently, additional mechanism other than the well-described inhibition of leukocyte recruitment due to selectin blockade may be involved in the resulting effects of bimosiamose treatment in our animal model. This hypothesis is supported by earlier reports discussing, in addition to selectin blockage, secondary immunomodulating effects of bimosiamose (Langer et al. 2004; Green et al. 2004; Toledo-Pereyra et al. 2004; Hicks et al. 2005). In our study, we did not investigate the mode-of-action of bimosiamose. As the aim of the study was to assess the overall efficacy of bimosiamose treatment, our exploratory data from the PP- and PN-model & encouraged us to proceed in evaluating the antipsoriatic activity of bimosiamose in patients.

Intralesional administration of bimosiamose was well tolerated and resulted in systemic antipsoriatic activity during treatment

Although several selectin antagonists have been effective in preclinical models, none of them performed satisfactorily in clinical trials (Sperandio et al. 2004; Schon et al. 2004). To evaluate the effects of bimosiamose in psoriatic patients, we performed an open-label pilot study. Five patients diagnosed with moderate to severe psoriasis were treated with bimosiamose by intralesional, subcutaneous injection (600 mg/day) over the treatment period

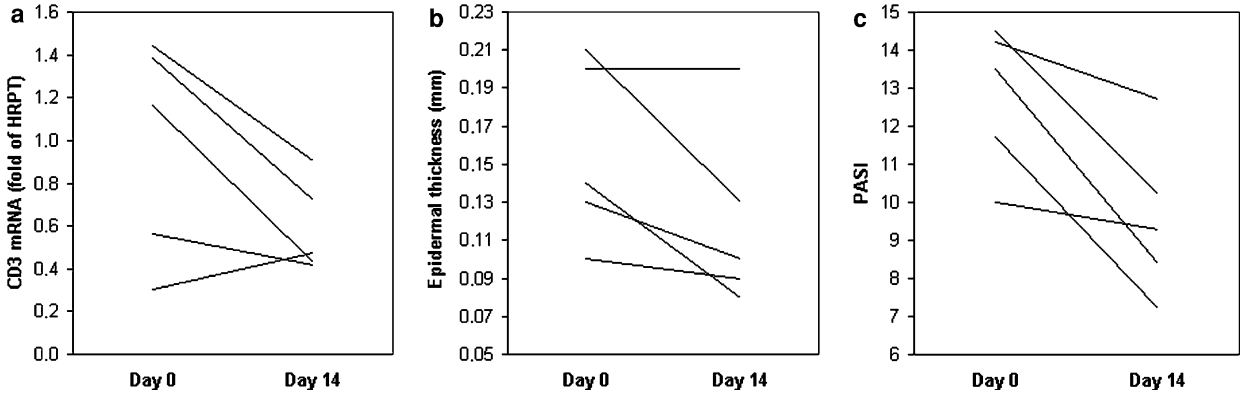

Fig. 4 Analysis of epidermal CD3 mRNA, epidermal thickness and PASI score in psoriasis patients before and after subcutaneous administration of bimosiamose. Bimosiamose (600 mg/day) was administered subcutaneously to psoriasis patients for 14 days. **a** The relative amount of CD3 mRNA in biopsies was analyzed for each patient before and after treatment. Demonstrated are the individual developments of the relative CD3 mRNA amount between day 0 and day 14. **b** On day 0 and 14, the epidermal thickness was measured. Demonstrated are the individual developments of the epidermis thickness between day 0 and day 14. **c** On day 0 and 14, the PASI score was analyzed for each patient. Demonstrated are the individual developments of the PASI score between day 0 and day 14. The *plotted lines* demonstrate individual patients

Table 1 Target skin lesion and control skin lesion assessment—Sum scores of erythema (E), induration (I) and desquamation (D) from pre-study to day 14

Grade	Target skin lesion				Control skin lesion			
	Pre-study		Day 14		Pre-study		Day 14	
	Sum score	E I D	Sum score	E I D	Sum score	E I D	Sum score	E I D
Slight	0	- - -	2	- 1 1	1	- - 1	2	1 1 -
Moderate	4	1 2 1	11	4 4 3	5	2 3 -	10	3 3 4
Marked	11	4 3 4	2	1 - 1	9	3 2 4	3	1 1 1

of 14 days. Laboratory and clinical findings were analyzed. To assess systemic bioavailability, serum levels of bimosiamose were analyzed pre- and post-dosing during the study. The maximum concentration was measured 1–2 h after administration, declining by approximately 30–50% at 6 h post-dosing. Values on day 2 to 13 (pre-dosing) indicated that a steady state was reached after the first 24 h dosing interval suggesting a systemic availability of the drug during the entire treatment period. The administration of bimosiamose was clinically well tolerated as analysis of safety parameters did not show any clinically relevant finding (data not shown). Treatment with bimosiamose reduced the epidermal lymphocyte infiltrate as suggested by up to 63% decrease of CD3 mRNA in the skin in four out of five patients (Fig. 4a). This was accompanied by up to 43% attenuation of epidermal thickness in four out of five patients (Fig. 4b). Interestingly, the same patient who showed no attenuation of CD3 mRNA was also unresponsive to treatment regarding epidermal thickness.

The clinical analysis of the PASI score showed a mean value ± SD before therapy of 12.8 ± 1.9 and at the end of the treatment of 9.6 ± 2.1. This decline was statistically significant ($P = 0.02$). Individual analysis of clinical improvement, e.g., decline in PASI score revealed an improvement in all five patients (Fig. 4c). The extent of improvement varied between individual patients (7, 11, 30, 38 and 38%) and did not correlate with the individual plasma levels of bimosiamose (data not shown). The results of assessment of target (injected) skin lesion and control (non-injected) skin lesion were similar suggesting that both treated and control lesion benefited from treatment with bimosiamose in a similar extend (Table 1).

In our study, we observed in vitro, in animal models of psoriasis as well as in psoriatic patients, consistent efficacy of the pan-selectin antagonist bimosiamose. Taking into account the low number of patients enrolled in the clinical study ($n = 5$) and the short treatment period of 14 days, the observed effectiveness and safety of bimosiamose as an antiinflammatory treatment suggest the need to perform advanced clinical trials of longer duration. In addition, the strategy of targeting more than one selectin in inflammatory skin disorders was previously supported by work showing efficacy for Efomycine M, a modified bacterial compound antagonizing E- and P-selectin, in animal models of psoriasis (Schon et al. 2002).

Taken together, using psoriasis as a T-cell mediated chronic inflammatory disorder, our study demonstrated for the first time that the therapeutic strategy of pan-selectin antagonism can be transformed from an experimental level in vitro via a disease model into a clinical setting (''from lab bench to bedside'').

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