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Efaluzimab in the treatment of psoriasis

The opening years of this millennium showed a substantial increase in the number of pharmaceutical and biotechnology companies developing new systemic therapies for psoriasis (8). Before 1980 most dermatologists regarded psoriasis primarily as a disease of epidermal keratinocyte hyperproliferation, and its attendant cutaneous inflammation as a secondary feature (8). Psoriasis vulgaris is one of the T-cell-mediated inflammatory diseases in humans. The pathogenesis of psoriasis is connected with activation of various leukocytes engaged in cellular immunity and with the development of T-cell-dependent inflammatory process in the skin (9). Subsequent acceleration of epidermal and vascular cells' growth in psoriasis lesions is believed as the secondary event (9). The evidences for considering psoriasis as a T-cell mediated dermatosis are numerous: 1) presence of activated T cells in the skin lesions, 2) cure of the disesase by bone-marrow transplantation from healthy persons and transfer of the disease by transplantation of bone marrow from psoriatic patients, 3) demonstration of the immunocytes impact by SCID mice experiments, and 4) therapeutic effects of immunosuppressants targeting lymphocytes, e.g. cyclosporin A (2). Critical steps in immunologic activation include Langerhans cell maturation, T-cell activation, differentiation and expansion of type 1 Th cells, their selective trafficking to skin, and induction of an inflammatory cytokine and cascade in skin lesions (11). Possibility of specifically inhibiting the antigen presenting cell (APC)-T cell interaction is one of the most attractive starting points for the development of new immunosuppressants. Some possibilities exist in the inhibition of T-cell activation (2). Various experimental therapies are based on the idea of blocking this activation by targeting lymphocyte-function-associated antigen-1 (LFA-1) using antibodies and fusion proteins as inhibitors (2,8). Among these antibodies, a humanized monoclonal antibody (hu 1124, efaluzimab), against the CD11a component of lymphocyte-function-associated antigen-1 is recently being carefully examined (8, 13). CD11a is a subunit of LFA-1, a cell surface molecule involved in T cell mediated immune responses (3). Leukocyte function-associated antigen 1, consisting of CD11a and CD18 subunits, plays an important role in T-cell activation and leukocyte extravasation (6). It has a key function in the development of the crucial steps of inflammation and tissue rejection. These include: (1) binding of leukocytes to endothelium; (2) trafficking through activated endothelium; and (3) costimulatory interactions between T lymphocytes and antigen presenting cells (4). Other names for this subunit of LFA-1 are Xanelin or Hu1124 (1,12).

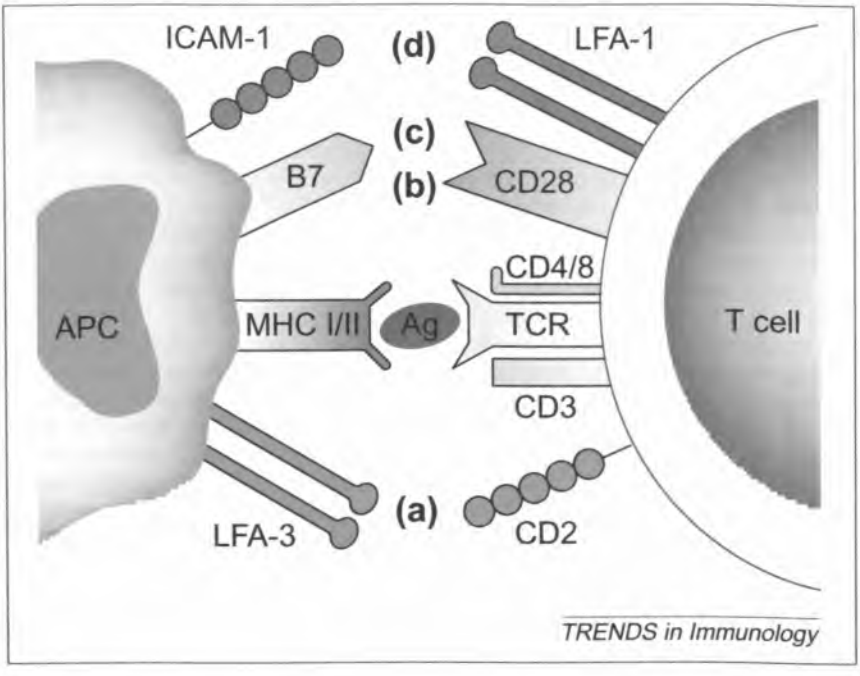

Fig. 1.[1] Special sites of action for inhibition of APC-T-cell interactions. Inhibition of the APC-T-cell interaction is one of the most attractive starting points for the development of new immunosuppressants. Possibilities exist in the inhibition of T-cell activation. This occurs through the TCR-CD3 complex after contact with a specific antigen, which is presented embedded in the MHC complex of APCs. MHC class I molecules also interact with CD8, whereas MHC class II molecules interact with CD4, defining corresponding T-cell subpopulations. For effective T-cell activation, these processes alone are insufficient and require adequate costimulation. The sites of action of various experimental therapies for blocking this costimulation are shown: (a) LFA-3TIP; (b) anti-B7; (c) CTLA-4; and (d) anti-LFA-1. Abbreviations: APC, antigen-presenting cell; CTLA-4, cytotoxic-T-lymphocyte-associate antigen 4; ICAM, intercellular adhesion molecule; LFA, leukocyte function-associated antigen; TCR, T-cell receptor

Papp et al. (13) reported that efaluzimab produced significant improvement in moderate or severe psoriasis in 19 of 75 patients treated intravenously once weekly for 8 weeks. This regime of treatment neither reduced the number of circulating lymphocytes nor had any serious side-effects in the short-term (8).

Multicentral intensive studies were carried out on the development of a humanized monoclonal antibody, hu1124 (anti-CD11a), which has the potential to treat psoriasis and

[1] Fig. 1 reprinted from publication TRENDS in Immunology Vol. 23 No. 1, Asadullah Khusru, Volk Hans-Dieter, Sterry Wolfram , *Novel immunotherapies for psoriasis*, 47-53, January 2002, with permission from Elsevier.

prevent organ transplant rejection. The III phase of clinical study has already been performed in the group of moderate to severe psoriasis patients (7).

Papp et al. (13) reported the interaction of CD11a (LFA-1) with various ICAM molecules. Anti-Cd 11a Ab can inhibit both the APC-T cell interaction and the adhesion of T cells to and/or their transendothelial migration since ICAM-1 (CD 54) is expressed on activated endothelial cells and APCs (10).

Gottlieb et al. (6) observed thirty-nine patients in the group of moderate to severe psoriasis, treated with intravenous infusions of efaluzimab, for 7 weeks from 0.1 mg/kg to 1.0 mg/kg weekly. Histological as well as clinical improvement were dose-related. The mean decrease in the PASI score was observed in the majority of the patients in relation to the dose category. Epidermal and dermal T-cell counts, epidermal thickness, and ICAM-1 and K16 expression decreased in categories of medium and highest dose but not in the subjects treated with the lowest dose of drug. Circulating lymphocyte counts increased in patients treated with higher doses. At doses of 0.3 mg/kg or more per week, intravenously administered efaluzimab produced significant clinical and histologic improvement in psoriasis, which correlated with sustained serum efaluzimab levels and T-cell CD11a saturation and down-modulation (6).

Bauer et al. (3) investigated the pharmacokinetics of hu1124. The subjects received a single dose from 0.03 to 10 mg/kg of hu1124 intravenously over 1–3 hr. As the dose of hu1124 was increased, the clearance decreased. In addition, treatment with hu1124 caused a rapid reduction in the level of CD11a expression on CD3-positive lymphocytes (T cells) to about 25% of pretreatment levels. One of the receptor-mediated pharmacokinetic/pharmaco-dynamic models which was developed describes the dynamic interaction of hu1124 binding to CD11a, resulting in the removal of hu1124 from the circulation and reduction of cell surface CD11a. The model accounts for the continually changing number of CD11a molecules available for removing hu1124 from the circulation based on prior exposure of cells expressing CD11a to hu1124. In addition, the model also accounts for saturation of CD11a molecules by hu1124 at drug concentrations of approximately 10 micrograms/ml, thereby reducing the clearance rate of hu1124 with increasing dose. Papp et al. (13) investigated whether treatment with anti-CD11a antibody provides clinical benefit to patients with moderate to severe plaque psoriasis. In total, 145 patients with minimum PASI scores of 12 and affected body surface area of 10% or more were sequentially enrolled into low-dose (0.1 mg/kg, n = 22) or high-dose (0.3 mg/kg, n = 75). The drug was administered intravenously at weekly intervals for 8 weeks. The treatment was well tolerated; mild to moderate flu-like complaints were the most common adverse events (13). White blood cell counts and lymphocyte counts transiently increased. Depletion of circulating lymphocytes did not occur. Anti-CD11a antibody administered intravenously in 8 weekly doses of 0.3 mg/kg was well tolerated and induced clinical and histologic improvements in psoriasis (13).

Gottlieb et al. (5) explored the immunobiologic and clinical effects of treating moderate to severe psoriasis vulgaris with a single dose of 0,03 to 10 mg/kg of humanized monoclonal antibody against CD11a (hu1124). Clinical (PASI estimation) and immunohistologic parameters (epidermal thickness, epidermal and dermal T-cell numbers, and ICAM-1 expression) were followed and estimated. Treatment with hu1124, at doses higher than 1.0 mg/kg carefully considered, completely blocks CD11a staining for at least 14 days in both blood and psoriatic plaques. At 0.3 to 1.0 mg/kg, T-cell CD11a staining was completely blocked; however, blockade lasted less than 2 weeks. Only partial saturation of either blood or plaque cellular CD11a was observed at doses of hu1124 between 0.01 and 0.1 mg/kg. This pharmacodynamic response was accompanied by decreased numbers of epidermal and dermal CD3 (+) T cells, decreased keratinocyte and blood vessel expression of ICAM-1, and epidermal thinning. Statistically significant drops in PASI compared with baseline were observed in the group with the highest dose as early as 2 weeks and after 3 and 4 weeks in the medium dose patients (5).

The treatment was well tolerated; mild to moderate flu-like complaints were the most common adverse events. White blood cell counts and lymphocyte counts transiently increased.

The depletion of circulating lymphocytes did not occur (13). The adverse events were mild at doses of 0.3 mg/kg or less and included mild chills, abdominal discomfort, headache, and fever. At a single dose of 0.6 mg/kg or higher, headache was the most common dose-limiting toxicity observed (5). Literature data indicate that targeting CD11a may improve psoriasis by inhibiting T-cell activation, T-cell emigration into the skin, and cytotoxic T-cell function.

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SUMMARY

We present a review of the literature concerning treatment of psoriasis with humanized monoclonal antibody (hu 1124, efaluzimab, Xanelin) against the CD11a component of lymphocyte-function-associated antigen-1 (LFA-1). Efaluzimab inhibits the interaction of CD11a (LFA-1) with various ICAM molecules. Because ICAM-1 (CD54) is expressed on activated endothelial cells and antigen presenting cells (APCs), the antibody inhibits both the APC-T cell interaction and the T- cell adhesion to endothelial cells, their subsequent activation, which results in decreasing of transendothelial migration. Treatment with Efaluzimab was well tolerated and the majority adverse events were dose-related. Adverse events were described as

mild at doses of 0.3 mg/kg or less and included mild chills, abdominal discomfort, headache, and fever (flu-like complaints), apart from this white blood cell counts and lymphocyte counts transient increase were observed. Headache was the most common dose-limiting toxicity observed at a single dose of 0.6 mg/kg or higher.

Efaluzimab w leczeniu łuszczycy

W pracy prezentujemy dane z literatury, dotyczące leczenia łuszczycy za pomocą humanizowanego przeciwciała monoklonalnego (hu 1124, efaluzimab, Xanelin) przeciwko antygenowi CD11a, stanowiącemu element cząsteczki LFA-1 (*lymphocyte function-associated antygen* – antygen związany z czynnością limfocytów). Efaluzimab hamuje wzajemne oddziaływania CD11a (LFA-1) i różnych cząsteczek ICAM (cząsteczki adhezji międzykomórkowej). Ponieważ aktywowane komórki śródbłonka oraz komórki prezentujące antygen (APCs) wykazują ekspresję ICAM-1 (CD54), przeciwciało to hamuje zarówno interakcje pomiędzy komórkami APC a limfocytami T, jak również adhezję limfocytów T do komórek śródbłonka oraz spowodowaną tym aktywację, co w rezultacie zmniejsza przezśródbłonkową migrację limfocytów. Leczenie Efaluzimabem było dobrze tolerowane, a większość działań ubocznych była zależna od dawki. Objawy uboczne były określane jako średnie przy dawce 0,3 mg/kg lub mniejszej i obejmowały łagodne dreszcze, zaburzenia żołądkowo-jelitowe, bóle głowy, gorączkę (objawy grypopodobne), poza tym obserwowano przejściowy wzrost liczby krwinek białych i limfocytów. Ból głowy był najczęściej obserwowanym objawem ubocznym, ograniczającym dawkę leku przy pojedynczej dawce 0,6 mg/kg lub większej.