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CCC: 0377-8282/2001

Alefacept

Antipsoriatic

Prop INN; USAN

BG-9273
BG-9712
LFA3TIP
LFA-3(92)IgG
Amevive™

Recombinant human LFA-3/IgG_1 fusion protein

1-92-LFA-3 (antigen) (human) fusion protein with immunoglobulin G_1 (human hinge-C_H2-C_H3 γ1-chain), dimer

CAS: 222535-22-0

EN: 197339

Production

LFA3TIP (alefacept) was constructed from the cDNA encoding the first domain of LFA3 gene and the cDNA encoding the C_H2-C_H3 domain of IgG_1. The cDNA encoding the signal peptide sequence of LFA3 and the first 92 amino acids of mature LFA3 flanked by a *Not*I site at the 5'-end and a *Sal*I site at the 3'-end was constructed by PCR from pHT16-6 cDNA (1). The cDNA encoding the C_H2-C_H3 domain of human IgG_1, including the hinge region, with a S*al*I site at the 5'-end and a *Not*I site at the 3'-end, was amplified by PCR on the RNA from COS-7 cells that were transfected with genomic IgG-encoding DNA, derived from a human genomic fibroblast library. The two obtained cDNAs were ligated together with the introduced *Sal*I sites and using the *Not*I sites on the outer ends of the resulting insert ligated into the expression vector pSAB132, generating the pSAB152 plasmid (2, 3).

Introduction

Psoriasis is an inherited chronic autoimmune inflammatory skin disease that afflicts 2-3% of the population worldwide and prevalence increases with increasing age. The disorder involves genetic, immunological and infectious factors and approximately 15% of all afflicted individuals develop inflammatory arthritis (4-6). The most common type of psoriasis is vulgaris or plaque psoriasis. Other existing forms include guttate, inverse, pustular and erythrodermic. Psoriasis is characterized by epidermal cell hyperproliferation, infiltration of inflammatory cells and angiogenesis resulting in erythematous plaques. A 40-fold increase in the number of epidermal mitotic cells is observed in addition to a decrease in the transit time through the living layer from approximately 12 to 2 days (7). Moreover, there are extensive changes in epidermal histology and gene expression comparable to that seen during wound healing. The nonliving cornified skin layer becomes thicker and disorganized and keratinocytes begin to express new structural proteins such as intermediate filament subunits keratins 6 and 16 and precursor proteins for the epidermal cornified envelope (4, 8-11).

Several different genes have been linked to psoriasis of which the majority are associated with the major histocompatibility complex (MHC) allele HLA-Cw6. In general, individuals suffering from psoriasis can be classified into two types: those with early onset of the disease (16-20 years) who show a clear family predisposition and those with late onset (55-60 years) where little family predisposition can be detected (4, 12, 13).

The pathology of psoriasis involves an interaction between inflammatory cells, particularly T cells and keratinocytes; thus, immunosuppressants can be effective as a treatment of the disease. T cells infiltrating psoriatic lesions include those with a memory-effector phenotype (CD45RO+) that express CD4 or CD8 markers. These cells preferentially secrete interferon-γ and low levels of IL-4 which is indicative of Th1 cells. The factor(s) which stimulate T-cell activation in psoriasis remain unclear. It is known that streptococcal A-induced throat infections can lead to guttate psoriasis and a structural relationship has been found between streptococcal protein M and keratin type I whereby T cells activated by streptococcal infection recognize the keratin in keratinocytes. The result is a cross-reactivity against keratinocytes (14-16). Other evidence suggests that the human papillomavirus type 5 (HPV5) may also be involved in the pathogenesis of psoriasis. A study demonstrated that HPV5 DNA was identified in the skin of 90% of patients suffering from psoriasis (17).

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Table I: T-cell activation inhibitors in development for psoriasis (Prous Science Drug R&D Backgrounders database).

Drug Name	Originator/Licensee	Mechanism of Action/Description	Status
1. Alefacept	Biogen	Recombinant LFA-3/IgG human fusion protein	Phase III
2. Efalizumab	Genentech/Xoma	Humanized anti-CD11a MAb	Phase III
3. Daclizumab*	Protein Design Labs.	Humanized anti-IL-2Rα MAb	Phase II
4. Denileukin diftitox**	Ligand	Diphtheria toxin-IL-2 fusion protein	Phase II
5. Visilizumab	Protein Design Labs.	Humanized anti-CD3 antibody	Phase II
6. HuMax-CD4	Medarex/Genmab	Anti-CD4 MAb	Phase II
7. IDEC-114	IDEC/Mitsubishi-Tokyo Pharm.	Anti-CD80 (anti-B7-1) MAb	Phase II
8. IDEC-131	IDEC/Eisai	Humanized anti-CD40L (anti-CD154) MAb	Phase II
9. IR-502	Immune Response	T cell receptor-based vaccine	Phase II
10. Siplizumab	BioTransplant/Medimmune	Humanized anti-CD2 MAb	Phase II
11. Cedelizumab	R.W. Johnson Res. Inst.	Humanized anti-CD4 MAb	Clinical Trials
12. IC-747***	Icos	CD11a (LFA-1) antagonist	Preclinical
13. LPD-519	Millennium	Proteasome inhibitor that suppresses the activation of NF-κB	Preclinical

1-92-LFA-3 (antigen) (human) fusion protein with immunoglobulin G_1 (human hinge-C_H2-C_H3 γ1-chain), dimer

(1)

Immunoglobulin G_1, anti-(human CD11a [antigen]) (human-mouse monoclonal hu1124, γ1-chain), disulfide with human-mouse monoclonal hu1124 light chain, dimer

(2)

Immunoglobulin G_1 (human-mouse monoclonal clone 1H4 γ-chain anti-human interleukin-2 receptor), disulfide with human-mouse monoclonal clone 1H4 light chain, dimer

(3)

N-L-Methionyl-387-L-histidine-388-L-alanine-1-388-toxin (*Corynebacterium diphtheriae* strain C7) (388-2')-protein with 2-133-interleukin 2 (human clone pTIL2-21a)

(4)

Immunoglobulin G_2, anti-(human antigen CD3) (human-mouse monoclonal HuM291 γ2-chain), disulfide with human-mouse monoclonal HuM291 κ-chain, dimer

(5)

Fully human IgG_1 anti-CD4 monoclonal antibody

(6)

Primatized(TM) anti-B7-1 (CD80) monoclonal antibody

(7)

Humanized monoclonal antibody that targets gp39 molecules (CD40 ligand, CD40L) on helper T cells

(8)

Combination of two peptides derived from T-cell receptors (Vβ3,Vβ13.1) in incomplete Freund's adjuvant (IFA)

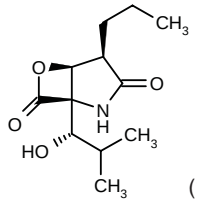
(9)

Humanized anti-CD2 monoclonal antibody, the humanized version of BTI-322

(10)

Immunoglobulin G_4, anti-(human CD4 [antigen]) (human-mouse monoclonal OKTcdr4a complementary determining region-grafted γ4-chain), disulfide with human-mouse monoclonal OKTcdr4a complementary determining region-grafted κ-chain, dimer

(11)



(13)

*Marketed for organ transplant rejection. **Marketed for cutaneous T-cell lymphoma. ***Structure not yet detected

Several therapies are currently available for psoriasis including treatment with methotrexate, retinoids and ciclosporin. However, safety concerns have restricted the clinical use of these agents. Topical therapies with varying mechanisms of actions are also available and include ultraviolet light, glucocorticoids, 1,25-dihydroxyvitamin D_3 analogs and the retinoid, tazarotene. Other therapeutics under development are the immunosuppressive biological macromolecules such as hu1124 (efalizumab), the humanized version of the murine anti-human CD11a monoclonal antibody (mAb) MHM24 (18). These macromolecules can block or suppress receptors required for T-cell activation. Research efforts are currently focusing on the discovery of monoclonal antibodies or fusion proteins specific for adhesion/signaling molecules to be used as immunotherapies. These new therapies are more selective and less toxic. Disruption of the different accessory molecule pathways (*e.g.*, CD2/lymphocyte function antigen-3 [LFA-3, CD58], ICAM-1/LFA-1, CD28/B7, VLA4/VCAM) that are involved at different points during T-cell activation enabling optimal T-cell responses results in inhibition of T-cell responses. Several of these agents

are shown in Table I (4). One such novel agent that has shown promise is a soluble LFA-3 construct in the form of a human Ig fusion protein. It is known as LFA3-IgG_1 or LFA3TIP (alefacept; Amevive™). LFA3TIP is a highly glycosylated protein dimer (115 kD) composed of the first LFA-3 extracellular domain fused to the hinge C_H2 and C_H3 regions of a human IgG_1. It has shown immuno-modulatory efficacy and was chosen for further development as a treatment for psoriasis.

Pharmacological Actions

Results from *in vitro* studies using a panel of LAF3TIP functional variants showed that the fusion protein LAF3TIP (0.5 and 5 μg/ml) inhibited the mixed lymphocyte reaction (MLR) of human peripheral blood lymphocytes (PBLs) isolated from healthy volunteers and stimulated by human JY B-cell tumor cells. This inhibition was dependent on the effector functions of the LAF-3 and C_H2 domain. Further analysis showed that the efficacy of LAF3TIP on T-cell responses required that the LAF-3 and C_H2 domains be expressed on the same molecule and that these domains bind to CD2 and FcγRI or FcγRIII, respectively. By forming an intercellular FcγR/CD2 bridge, LAF3TIP induced the cytolysis of CD2+ cells by human PBLs *in vitro*. LFA3TIP also inhibited tetanus toxoid-, hepatitis B surface antigen-, anti-CD3 mAb-, Con A- and phytohemagglutinin (PHA) P-induced memory T-cell proliferation in addition to xenogeneic (murine A20 cells) and allogeneic MLRs. Similarly, studies using spleen cells isolated from transgenic human CD2 transgenic Tg mice showed that administration of LAF3TIP (100 μg i.p.) in vivo inhibited T-cell proliferation in response to PHA. The mechanism of action of LAF3TIP was shown to be different from that of anti-LFA-3 or anti-CD2 mAbs, which inhibit T-cell responses by blocking LFA-3/CD2 binding, in that LAF3TIP also induced T-cell unresponsiveness in cases were T-cell activation was independent of CD2/LFA-3 interactions (3, 19).

An *in vitro* study attempting to optimize the expression efficacy when preparing large amounts of LFA3TIP revealed differential effects of the resulting agent depending on the cell line chosen for production. LFA3TIP produced from either CHO or murine myeloma (NS-0) cell lines appeared to be comparably effective in CD2 receptor binding and T-cell assays. However, reductions in CD2+ lymphocytes from mice or baboons administered NS-0-derived LFA3TIP (1, 10 or 100 μg i.v.) were less sustained than decreases seen in animals administered the same doses of CHO-derived LFA3TIP. Further analysis of the agents revealed that NS-0-derived LFA3TIP was cleared more rapidly from the circulation and possessed a different pattern of glycosylation. NS-0-derived LFA3TIP was less extensively sialylated, partially due to alpha-galactosyl capping of lactosamine moieties in the N-linked glycans of NS-0-derived LFA3TIP. In contrast to the NS-0-derived agent, CHO-derived LFA3TIP, following enzymatic desialylation, yielded a glycoprotein that when administered to both mice and baboons displayed an evanescent serum profile. Results indicate a differential correlation between *N*-acetylneuraminic acid capping and clearance rates of agents derived form the 2 cell lines (20).

LAF3TIP was also shown to bind to PBLs from baboons, rhesus and cynomolgus monkeys, indicating that nonhuman primates may be an effective model for examining the efficacy of the agent. In this regard, studies in which baboons were administered the fusion protein (3 mg/kg/day i.v. for 12 days) revealed that LAF3TIP accumulated over the dosing period with a trough C_{max} of 60 μg/ml seen after 8-12 injections and 10 μg/ml detected 10-14 days postdosing. Examination of serum samples from treated animals showed that LAF3TIP successfully bound to human CD2 transfected CHO cells. Administration of the agent was found to cause a decrease in white blood cell counts within the first hour of the first injection; this effect was sustained for the first 48 h of dosing and found to be due to T-cell depletion. In contrast, a concurrent increase in B cells was observed, indicating that the majority of the lymphocytes still present were B cells. Continued dosing did not worsen lymphocytopenia although lymphocyte reductions (45-85%) were sustained throughout the dosing period. Although treatment with LAF3TIP did not alter expression of CD3, CD4 and CD8 T-cell markers, a reduction in CD2 expression of PBLs was observed by day 3 of treatment; a mean decrease in CD2 expression of 60% was seen by days 8-10. No adverse effects of the agent were observed on body weight, hematological parameters, urinalysis or clinical signs and no antibodies specific for the agent were detected (21).

The efficacy of LAF3TIP (3 mg/kg i.v. for 12 days starting 2 days prior to transplantation) in prolonging primate cardiac allograft survival was demonstrated in a study using baboon recipients of heterotopic cardiac allografts. Peak serum levels of the agent of about 100 μg/ml were observed following 7-9 injections and a concentration of 10 μg/ml was sustained for 1-2 weeks postdosing. Treatment with LAF3TIP delayed graft rejection (18 ± 5.3 *vs.* 10.6 ± 2.3 days in human IgG-treated controls). Moreover, grafts from treated animals exhibited a reduced incidence of coronary endothelialitis (*i.e.*, infiltration of inflammatory cells, particularly lymphocytes) as compared to control animals. No renal or hepatic toxicities were observed (22).

Pharmacokinetics

The pharmacokinetics of LFA3TIP were reported from 2 studies conducted in baboons. In the first study, the pharmacokinetic parameters obtained following LFA3TIP administration (1 or 10 mg/kg i.v. every 72 h for 648 h) were best fitted to a nonlinear, saturable, 2-compartmental model which allowed for a dose-dependent exponential decay. Results showed that weight significantly correlated with distribution volume of the central compartment

Table II: Pharmacokinetic parameters of alefacept (Prous Science Integrity database).

Species	Dose	$t_{1/2}$ (days)	Cl (ml/h)	Vd_c (l)	Vd_p (l)	Vss (l/kg)	Ref.
Baboon (CHO/NS-0)[a]	3 mg/kg s.d.	5.5/4.9	–	–	–	–	20
Mice (CHO/NS-0)[a,b]	3 mg/kg s.d.	–	2.1/31.0[e]	–	–	–	
Baboon	1 or 10 mg/kg q72h x 27 days	–	5.5	0.04[f]	0.6	–	23
Humans	4-225 µg/kg 30 min i.v. infusion	–	18.8 (0.24)[d]	3.7	1.9	0.07	25
Humans[c]	5-75 µg/kg once weekly	37.1	0.18[e]	4.3	2.2	–	26

[a]Product derived from CHO (Chinese hamster ovary) or NS-0 (murine myeloma) cells; [b]human CD2 transgenic mice; [c]patients with chronic plaque psoriasis; [d]ml/h/kg in brackets; [e]ml/h/kg; [f]l/kg.

(V1). Values obtained for clearance, V1, distribution volume of the peripheral compartment (V2) and intercompartmental clearance were 0.0055 l/h, 0.0392 l/kg, 0.5910 l and 0.0163 l/h, respectively. Pharmacodynamic point estimates of K_{max} and K_m were also obtained in this study and were 0.0047 ± 0.0009 h^{-1} and 16.8 ± 9.38 mg/l, respectively (23).

Results from the second pharmacokinetic study conducted in baboons administered multiple i.v. bolus doses of LFA3TIP (0.3-10 mg/kg) also fit a 2-compartmental model. Weight and creatinine were found to be covariants for clearance and weight affected V1; no covariants tested including weight, gender, albumin and creatinine correlated with intercompartmental clearance. The values obtained for clearance, V1, V2 and intercompartmental clearance were 0.0015 ± 0.00027*W l/h, 0.19 ± 0.22*W l, 0.041*W l and 0.012 l/h, respectively, where W is weight. The interanimal coefficient of variation was 23.2, 21.4, 30.1 and 45.5%, respectively, with a residual error of 38, 13.1 and 12.8% obtained for concentrations of 0.50, 50 and 500 µg/ml, respectively (24).

The pharmacokinetics of single-dose LFA3TIP (0.004-0.225 mg/kg i.v.) administered to 24 healthy volunteers were reported and found to fit a 2-compartmental model with first-order elimination from V1. Analysis of covariants including weight, height, age and dose showed that height correlated with V2 and dose with intercompartmental clearance in the full population model; no covariants were included on clearance or V1. Thus, no dose-dependency was observed for total clearance, V1 or V2. Values obtained for clearance, V1, V2 and intercompartmental clearance were 0.0188 l/h, 3.70 l, 1.92 l and –0.143*dose + 0.0648 l/h, respectively. Intersubject coefficients of variations were 24.6, 22.1, 50.9 and 69.6%, respectively, and residual errors were 15.7 and 10.2% for 150 and 4500 ng/ml, respectively (25).

The pharmacokinetics of once-weekly LFA3TIP (0.005-0.075 mg/kg/week i.v. for 8 weeks) were reported from a study conducted in 24 patients with chronic plaque psoriasis. The pharmacokinetic data obtained fit a 2-compartmental model and revealed that serum clearance of the agent was dependent on weight and age; no correlations were observed between distribution volumes and age, weight, height or body mass index. Mean serum clearance was approximately 0-18 ml/h/kg and V1, V2 and elimination $t_{1/2}$ values were about 4.3 l, 2.2 l and 890 h, respectively. The residual error obtained ranged from 18-32%. Results indicate that dose adjustments are not required with once-weekly dosing for age or weight (26).

The pharmacokinetic parameters of LFA3TIP in several animal species and humans are given in Table II.

Clinical Studies

The selectivity of multiple-dose LFA3TIP (12 weekly i.v. boluses) on peripheral memory-effector (CD45RO+) T cells over naive (CD45RA+) T cells was demonstrated in a randomized, placebo-controlled, double-blind, phase II study conducted in 124 patients with chronic plaque psoriasis. Reversible, dose-dependent decreases in CD2+, CD4+ and CD8+ lymphocytes were observed with treatment; CD19+ lymphocytes were not affected. Greater reductions in lymphocytes with memory-effector phenotypes (*i.e.*, CD4+ -CD45RO+ and CD8+ -CD45RO+) were observed while naive T-cell phenotypes (CD4+ -CD45RA+ and CD8+ -CD45RA+) were relatively unaffected by treatment. This selectivity of the agent was probably due to the increased expression of CD2 on CD45RO+ cells. The decrease in memory-effector T cells correlated with the degree of clinical improvement observed during 12 weeks postdosing. Of the 53% of patients who exhibited significant clinical improvement, 23% improved by 90% after the last dose. Treatment with the agent was well tolerated with a similar incidence of infections observed in treated and placebo groups. Results from this study also demonstrated a long duration of clinical response following treatment with LFA3TIP for 12 weeks. At 12 weeks postdosing, 43% of the patients achieved a 75% or greater decrease from baseline in Psoriasis Area and Severity Index (PASI) scores and 23% were clear or almost clear according to the Physician Global Assessment (PGA); 91 and 100%, respectively, of these patients elected to continue on to a retreatment study. The median time to retreatment after the last LAF3TIP dose in these subjects was 8 months (ranging from 5-17 months) (27-29) (Box 1).

The efficacy and tolerability of LFA3TIP were also evaluated in single-dose (0.005, 0.025, 0.050 or 0.075 mg/kg i.v. once weekly for 8 weeks) and multiple-dose (2 i.v. injections of 0.05, 0.1 or 0.15 mg/kg once every 4 weeks) trials in 24 and 18 patients with chronic plaque psoriasis, respectively. Treatment was well tolerated with

Box 1: Alefacept in patients with plaque psoriasis (29) [Prous Science Integrity database].

Design	Randomized, double-blind, placebo-controlled clinical study
Population	Patients with moderate to severe chronic plaque psoriasis (n = 124)
Treatments	Alefacept, i.v. bolus 1x/wk x 12 wks Placebo
Results	Psoriasis Area Severity Index reduction ≥ 75% @ 24 wks: A (53/124 [42.7%]) Clear/almost clear of psoriasis by Physician Global Assessment @ 24 wks: A (29/124 [23.4%])
Conclusions	Treatment with alefacept for 12 wks produced a long-lasting clinical response in patients with moderate to severe chronic plaque psoriasis

no serious adverse events related to LFA3TIP observed. All treated patients displayed a transient dose-dependent reduction in the absolute number of peripheral lymphocytes with CD2+, CD4+ and CD8+ lymphocytes affected; CD19+ lymphocytes were not altered. Moreover, greater reductions were observed in memory-effector T cells with CD4+ -CD45RO+ and CD8+ -CD45RO+ phenotypes over naive phenotypes (CD4+ -CD45RA+ and CD8+ -CD45RA+), indicating a selectivity of the agent for memory-effector T cells (30).

An ongoing, multicenter, open-label study is being conducted to determine the efficacy, tolerability and immunogenicity of subsequent LFA3TIP treatment in 185 patients with moderate to severe chronic plaque psoriasis who participated in previous phase II dose-finding or dose-ranging studies (31).

Significant results have recently been reported from 2 multicenter, double-blind, placebo-controlled phase III trials conducted in more than 1100 patients with moderate to severe plaque psoriasis (covering at least 10% of their total body surface area). The primary endpoint was a 75% or greater improvement in PASI scores 2 weeks after completion of 12 weeks of i.m. or i.v. LFA3TIP treatment. Of those patients who received 2 i.v. courses, 71 and 40% achieved a 50% or greater or 75% or greater decrease, respectively, in baseline PASI scores. Improvement measured by PASI score was correlated with a reduction in CD45RO+ cells. In addition, LAF3TIP-treated groups showed significant improvements in quality-of-life according to the Dermatology Life Quality Index (DLQI). The incidence of adverse events was similar in both LFA3TIP and placebo groups of which the most common in the LAF3TIP groups were accidental injury, headache, pruritus, infection (*e.g.*, common cold, folliculitis), pharyngitis and rhinitis (32).

The efficacy of LAF3TIP as a treatment in scleroderma and rheumatoid arthritis is currently being investigated in pilot studies. Biogen expects to file for both FDA and EMEA approval of Amevive™ in the second half of 2001 (32).

Manufacturer

Biogen, Inc. (US).

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