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hu1124

Antipsoriatic
Treatment of Transplant Rejection

Efalizumab
anti-CD11a MAb
Humanized MHM24
Xanelim™

Immunoglobulin G1, anti-(human CD11a [antigen]) (human-mouse monoclonal hu1124, γ_1-chain), disulfide with human-mouse monoclonal hu1124 light chain, dimer

CAS: 214745-43-4

EN: 236376

Introduction

Psoriasis is an inherited chronic autoimmune inflammatory skin disease affecting 2-3% of the world's population. An increase in incidence is observed with increasing age. The disease is a complex disorder involving genetic, immunological and infectious factors and approximately 15% of all afflicted individuals develop inflammatory arthritis (1-3). The disease 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 (4). Moreover, there are extensive changes in epidermal histology and gene expression. 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. The changing pattern of expression associated with psoriasis is comparable to that seen during wound healing (1, 5-8).

The most common type of psoriasis is vulgaris or plaque psoriasis. Other existing forms include guttate, inverse, pustular and erythrodermic. 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, there are 2 types of patients suffering from psoriasis: 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 (1, 9, 10).

The pathology of psoriasis involves an interaction between inflammatory cells, particularly T cells, and keratinocytes; thus, immunosuppressive treatment can be effective as a treatment of the disease. T cells infiltrating psoriatic lesions include those with a memory phenotype (CD45R0+) that express CD4 or CD8 markers. These cells preferentially secrete interferon-gamma 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 (11-13). 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 (14).

Several therapies are 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. These macromolecules can block or suppress receptors required for T-cell activation. Several of these agents are shown in Table I. One such agent, hu1124 (efalizumab), is the humanized version of the murine anti-human CD11a monoclonal antibody MHM24, in which 4 residues in one of the complementarity-determining regions (CDR-H2) in the variable heavy domain have been changed (15, 16). CD11a is a subunit of the

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Table I: Compounds that block T cell activation under clinical investigation for the treatment of psoriasis (Prous Science Drug R&D Backgrounders database).

Compound	Company	Description	Phase
hu1124 (Efalizumab)	Genentech/Xoma	Humanized anti-CD11a MAb	III
Alefacept (Amevive™)	Biogen	Recombinant human LFA-3/IgG fusion protein	III
HuMax™-CD4	Medarex/Genmab	Humanized anti-CD4 MAb	II
MEDI-507	Medimune/BioTransplant	Humanized anti-CD2 MAb	I/II
IDEC-114	IDEC/Mitsubishi-Tokyo Pharma.	Primatized anti-CD80 MAb	II
IDEC-131	IDEC/Eisai	Humanized anti-CD40L MAb	II
IR-502	Immune Response Corp.	T-cell receptor peptide vaccine	II
Daclizumab	Protein Design Labs	Humanized anti-IL-2Rα MAb	II
Denileukin diftitox	Ligand	Diphtheria toxin/IL-2 fusion toxin	II
HuM291 (Nuvion™)	Protein Design Labs	Humanized anti-CD3 MAb	I/II
Cedelizumab	Johnson & Johnson	Humanized anti-CD4 MAb	I/II
IC-747	Icos	LFA-1 antagonist	PC

adhesion molecule LFA-1 ($\alpha L\beta_2$ integrin) present on leukocyte surfaces. CD11a binds to ICAM-1 present on endothelial cells, keratinocytes and antigen-presenting cells and the CD11a/ICAM-1 interaction is involved in leukocyte extravasation into tissue and T-cell costimulation. hu1124 has been shown to effectively block migration of T cells into the psoriatic plaque and has been selected for further clinical development.

Pharmacological Actions

The binding affinity of hu1124 for chimpanzee and human CD11a was examined *in vitro* with similar results obtained for both species. The K_d values for human and chimpanzee were 0.114 and 0.148 μg/ml, respectively. Saturation was reached at a dose of 10 μg/ml (15, 17).

Preclinical investigation of hu1124 has also included examination of the agent's pharmacokinetics in chimpanzees. Results from a study conducted in healthy chimpanzees administered the agent (0.5-10 mg/kg) i.v. showed that plasma levels of the agent could be characterized into 3 phases. After administration of 8 mg/kg hu1124, levels decreased rapidly with a half-life of 0.4 days. The rate then decreased to an elimination β half-life of approximately 10 days. Subsequently, when plasma levels decreased to below 3 μg/ml, clearance rates increased to quickly eliminate any remaining traces of the agent. Treatment with hu1124 caused a rapid decrease in CD11a on the surface of circulating CD3+ T cells, CD19+ B cells and CD56+ natural killer cells, with expression declining to 20% of baseline by 24 h postdosing; CD11a levels were suppressed until the drug was eliminated from the circulation and full recovery was observed 7-10 days later (17).

Clinical Studies

Pharmacokinetics and pharmacodynamics

The pharmacokinetics of hu1124 have also been examined in patients with moderate to severe plaque psoriasis. A multicenter, open-label, dose-escalating single-dose phase I trial in 31 patients with moderate to severe plaque psoriasis administered hu1124 (0.03, 0.1, 0.3, 0.6, 1, 2, 3 or 10 mg/kg) as an i.v. infusion over 1-3 h and used noncompartmental analysis to derive the pharmacokinetic parameters of the agent. As the dose increased from 0.1 to 2 mg/kg, clearance decreased from 322 ml/day/kg to approximately 11 ml/day/kg; clearance did not markedly decrease when doses were increased from 2 to 10 mg/kg (6.6 ml/day/kg). Treatment with the agent resulted in a decrease in CD11a expressed on circulating lymphocytes to a level 25-30% that of baseline. As seen with chimpanzees, when circulating levels of the agent decreased to below 3 μg/ml, the agent was rapidly eliminated and expression of CD11a normalized within 7-10 days. Single doses greater than 1 mg/kg completely blocked CD11a expression for more than 14 days while doses of 0.3-1 mg/kg suppressed the integrin for 2 weeks or less. Treatment had no effect on the number of circulating T or B lymphocytes. Those patients receiving doses greater than 1 mg/kg also displayed the highest frequency of lesional T cells with CD11a blockade; lesional T-cell blockage was even observed at day 28 (17, 18) (Box 1).

This study also reported that hu1124 treatment induced significant reductions in epidermal thickness and the number of epidermal and dermal T cells in plaques (epidermal and dermal CD3+ T cells on days 14). Results suggest that the agent may reduce T-cell trafficking into psoriatic skin lesions. hu1124 treatment was also associated with a reduction in ICAM-1, indicating a possible decrease in the production of inflammatory cytokines from plaques (17, 18).

An additional open-label study conducted in patients with moderate to severe plaque psoriasis examined the pharmacokinetics of hu1124 (0.5-2 mg/kg) administered s.c. as 8 weekly injections. Results showed that although the bioavailability of s.c. hu1124 was reduced (by 35%) as compared to i.v. hu1124, similar improvements in psoriatic symptoms were observed with s.c. delivery although accompanied by fewer adverse events. Peak levels of hu1124 were detected at 1-3 days. As doses increased

Box 1: Effects of efalizumab on the immunobiology and clinical activity of psoriasis (18) [Prous Science CSline database].

Design	Multicenter, dose-finding, open clinical study
Population	Patients with moderate to severe psoriasis (n = 31)
Treatments	Efalizumab, 0.03 mg/kg i.v. infusion s.d. Efalizumab, 0.1 mg/kg i.v. infusion s.d. Efalizumab, 0.3 mg/kg i.v. infusion s.d. Efalizumab, 1.0 mg/kg i.v. infusion s.d. Efalizumab, 3.0 mg/kg i.v. infusion s.d. Efalizumab, 10 mg/kg i.v. infusion s.d.
Withdrawals	E1: 1
Adverse Events	E ≥ 0.3: headache 4/16 (25.0%), worsening psoriasis 5/16 (31.3%), chills 2/16 (12.6%), infection 4/16 (25.0%), fever 1/16 (6.3%), pain 4/16 (25.0%), pruritus 4/16 (25.0%) E ≥ 0.6: headache 8/15 (53.3%), worsening psoriasis 6/15 (40.0%), chills 8/15 (53.3%), infection 4/15 (26.7%), fever 6/15 (40.0%), nausea 5/15 (33.3%), pain 1/15 (6.7%), pruritus 1/15 (6.7%)
Results	Rate of patients with efalizumab complete saturation on peripheral T cells (%): E >1.0 (100) ≥ E0.3-1.0 (100) > E0.03-0.1 Rate of patients with efalizumab complete saturation on T cells (%) @ 14 d: E>1.0 (80.0) > E0.3-1.0 (46.7) > E0.03-0.1 (0) Rate of patients with efalizumab complete or partial saturation on T cells (%) @ 14 d: E>1.0 (100) > E0.3-1.0 (80.0) > E0.03-0.1 (25.0) Rate of patients with efalizumab complete or partial saturation on lesional T cells (%) @ 14 d: E>1.0 (100) > E0.3-1.0 (20.0) > E0.03-0.1 (0) Rate of patients with normal total immunoglobin to bacteriophage oX-174 (%) @ 14 d: E0.03-0.1 (75.0) > E0.3-1.0 (12.5) > E>1.0 (0) Rate of patients with suppressed IgG production to bacteriophage oX-174 (%) @ 14 d: E>1.0 (100) > E0.3-1.0 (87.5) > E0.03-0.1 (25.0) Rate of patients with reduction in PASI score @ 2-4 wks: E>1.0 > E0.03-0.1; E0.3-1.0 (87.5) > E0.03-0.1 (25.0) Erythema thickness @ 14 d: baseline > E0.3-1.0 [p <0.001]; @ 28 d: baseline > E0.3-1.0 [p <0.001]; @ 14 d: baseline > E>1.0 [p <0.05]; @ 28 d: baseline > E>1.0 [p <0.05] Epidermal CD3+ at plaque T cells @ 14 d: baseline > E0.3-1.0 [p <0.01]; @ 28 d: baseline > E0.3-1.0 [p <0.05] Dermal CD3+ at plaque T cells @ 14 d: baseline > E0.3-1.0 [p <0.01]; @ 14 d: baseline > E>1.0 [p = 0.03]
Conclusions	Efalizumab may be effective in moderate to severe psoriasis

from 0.5 to 2 mg/kg, peak and trough plasma levels increased from 3.4 to 18.1 μg/ml and 1.7 to 9.6 μg/ml, respectively. hu1124 could be detected in plasma for 10-58 days following the final injection. Treatment reduced CD11a expression on circulating T cells by approximately 75% and increased lymphocyte counts 2-fold; these levels were normalized once the drug was eliminated (19).

The pharmacokinetics and pharmacodynamics of hu1124 (0.7 mg/kg s.c. followed by 11 weekly injections of 1, 2 or 4 mg/kg) were also examined in an open-label study conducted in patients with moderate to severe plaque psoriasis. Peak plasma anti-CD11a levels were observed 1-5 days postinjection with levels increasing from 5.9 to 14.8 μg/ml with the 1 and 2 mg/kg doses, respectively. Mean trough levels increased from 4.1 to 32.4 μg/ml and average bioavailability increased from 26 to 44% as the dose increased from 1 to 4 mg/kg. Preliminary analysis has revealed that patients from all dose groups displayed a decrease of approximately 75% in the expression of CD11a on circulating T cells and a more than 97% reduction in available anti-CD11a binding sites. In addition, total circulating lymphocytes almost doubled with treatment; while T cells slightly increased, B cell and monocyte proportions were unaltered by treatment. Following clearance of the agent on day 133, NK cells were slightly decreased and CD11a expression and lymphocyte counts returned to baseline (20-22) (Box 2).

An open-label study conducted in 45 patients with moderate to severe plaque psoriasis examined the pharmacodynamics of hu1124 (1 or 2 mg/kg s.c. for 8 weeks). Both doses resulted in an almost doubling of circulating lymphocytes 2-7 days after the first dose which could be detected until day 6 after the last dose; the proportion of circulating CD19+ B and CD3+ T cells was unaltered by treatment. Skin biopsies taken at 28 days revealed mean decreases in epidermal CD3+ T cells and a reduction in available T-cell CD11a. At the end of treatment, dermal T-cell counts were reduced by approximately 60% with both doses (23) (Box 3).

Safety and efficacy

The efficacy of hu1124 (1 or 2 mg/kg s.c. for 8 weeks) was demonstrated in an open-label study conducted in 45

Box 2: Efficacy of efalizumab in patients with moderate to severe plaque psoriasis (22) [Prous Science CSline database].

Design	Open, multicenter clinical study
Population	Patients with moderate to severe plaque psoriasis (n = 61)
Treatments	Efalizumab, 1.0 mg/kg/wk s.c. [titrated from 0.7 mg/kg/wk] x 12 wks (n = 20) Efalizumab, 2.0 mg/kg/wk s.c. [titrated from 0.7 mg/kg/wk] x 12 wks (n = 20) Efalizumab, 4.0 mg/kg/wk s.c. [titrated from 0.7 mg/kg/wk] x 12 wks (n = 21)
Results	PASI score reduction ≥ 50% rate (%) @ 1 wk: 61-88 (across the 3 dose groups) PASI score reduction ≥ 75% rate @ 12 wks: E4 (9/21 [42%]) ≥ E1 (6/20 [30%]) ≥ E2 (5/20 (25%]) Improvement as judged by Physician Global Assessment scored as excellent rate (%): 25-50 (across the 3 dose groups)
Conclusions	Weekly subcutaneous administration of efalizumab for 12 weeks was convenient, well tolerated and markedly improved moderate to severe plaque psoriasis

Box 3: Effects of efalizumab on T-cell trafficking in patients with psoriasis (23) [Prous Science CSline database].

Design	Open clinical study
Population	Patients with moderate to severe psoriasis (n = 45)
Treatments	Efalizumab, 1.0 mg/kg s.c. x 8 wks (n = 21) Efalizumab, 2.0 mg/kg s.c. x 8 wks (n = 24)
Results	Rate of patients with >90% improvement in PASI @ 8 wks: E2 (15/24 [62%]) ≥ E1 (11/21 [52%]) Number of accesible efalizumab binding sites on circulating T cells, change @ 48 h: E (–95%) Epidermal CD3 T-cell count, change @ 28 d: E2 (–55%) > E1 (–27%); change @ 9 wks: E2 (–63%) ≥ E1 (–58%) Dermal T-cell count, change @ 8 wks: E (–60%)
Conclusions	Efalizumab may inhibit cutaneous T-cell trafficking in moderate to severe psoriasis

patients with moderate to severe plaque psoriasis. At the end of treatment, 52 and 62% of the patients treated with 1 and 2 mg/kg, respectively, showed a 50% improvement or greater in Psoriasis Area and Severity Index (PASI) scores from baseline (20). Similar results were reported from another study conducted in 55 patients with psoriasis who were treated with 8 s.c. doses/week (0.5, 0.5-1, 0.7-1.5 or 1-2 mg/kg). Treatment was well tolerated and of the 24 patients treated with the highest doses, 7 (29.2%) showed reductions of 75% or more in PASI scores by the end of the treatment period. Improvements were also observed in target lesion assessment scores (scale of 0-4) with mean decreases of –1.2, –1.7 and –1.3 in scaling for erythema, thickness and scaling, respectively. Mild acute adverse events (*i.e.*, fever, headache, nausea, chills, myalgia) were seen within 48 h of dosing in 37% of the patients; a higher incidence of adverse events was generally noted following the first dose after which a decrease was seen even with escalated dosing (24) (Box 4).

The efficacy and safety of hu1124 (0.01-10 mg/kg i.v. infusion over 1-3 h) were demonstrated in a multicenter, open-label, dose-escalating, single-dose phase I trial in 31 patients with moderate to severe plaque psoriasis. Patients treated with doses of 0.3-1 mg/kg and doses greater than 1 mg/kg displayed significant reductions in PASI scores from baseline at weeks 3-4 and 2-10, respectively; no significant change in scores was seen in patients treated with doses of 0.01 or 0.1 mg/kg. While only mild adverse events (i.e., chills, abdominal discomfort, headache, fever) were observed at doses of 0.3 mg/kg or less, doses of 0.6 mg/kg or higher were associated with reversible moderate to severe adverse events (*i.e.*, headache, chills, fever, nausea) of which headache was the most common and the dose-limiting toxicity. None of the patients presented antibody to hu1124 and all patients displayed normal primary antibody responses (predominantly IgM) to bacteriophage phiX174. However, 2/8, 14/16 and 6/6 patients administered 0.01 or 0.1 mg/kg, 0.3-1 mg/kg and > 1 mg/kg, respectively, showed impaired switching from IgM to IgG. However, further studies are required to determine if this dysfunction is of clinical relevance (18).

A multicenter, single-dose study conducted in 39 patients with moderate to severe psoriasis showed the tolerability and dose-dependent efficacy of hu1124 (7 i.v. doses: 0.1 mg/kg every other week [group I]; 0.1 mg/kg/week [group II]; 0.3 mg/kg/week [group III]; 0.3, 0.4 then 0.6 mg/kg for the remaining weeks [group IV]; or 0.3, 0.4, 0.6 then 1 mg/kg for the remaining weeks [group V]). No clinical or histological responses were observed in patients in groups I and II. However, a 34, 34 and 52%

Box 4: Clinical and histologic effects of efalizumab in patients with psoriasis (24) [Prous Science CSline database].

Design	Multicenter, dose-finding clinical study
Population	Patients with moderate to severe psoriasis (n = 55)
Treatments	Efalizumab, 0.5 mg/kg s.c. 1x/wk x 8 wks Efalizumab, 0.5-1.0 mg/kg s.c. 1x/wk x 8 wks Efalizumab, 0.7-1.5 mg/kg s.c. 1x/wk x 8 wks Efalizumab, 1.0-2.0 mg/kg s.c. 1x/wk x 8 wks
Adverse Events	E: 37% [mild to moderate fever, headache, nausea, chills, myalgia]
Results	Rate of patients with reduction > 75% in PASI score @ 8 wks: E (7/24 [29.2%]) Erythema score (0-4), change @ 8 wks: E (–1.2) Thickness score (0-4), change @ 8 wks: E (–1.7) Healing score (0-4), change @ 8 wks: E (–1.3)
Conclusions	Efalizumab was safe and effective in moderate to severe psoriasis

Box 5: Efficacy of efalizumab in patients with moderate to severe psoriasis (25) [Prous Science CSline database].

Design	Multicenter, dose-finding, crossover clinical study
Population	Patients with moderate to severe psoriasis (n = 39)
Treatments	Efalizumab, 0.1 mg/kg i.v. 1x/2wk x 6 wks Efalizumab, 0.1 mg/kg i.v. 1x/wk x 6 wks Efalizumab, 0.3 mg/kg i.v. 1x/wk x 6 wks Efalizumab, 0.3 mg/kg i.v. 1x/wk x 1 wks → Efalizumab, 0.4 mg/kg i.v. 1x/wk x 1 wks → Efalizumab, 0.6 mg/kg i.v. 1x/wk x 4 wks Efalizumab, 0.3 mg/kg i.v. 1x/wk x 1 wks → Efalizumab, 0.4 mg/kg i.v. 1x/wk x 1 wks → Efalizumab, 0.6 mg/kg i.v. 1x/wk x 1 wks → Efalizumab, 1.0 mg/kg i.v. 1x/wk x 3 wks
Results	PASI score, change @ 42 d: E1.0 (–52%) ≥ E0.6 (–34%) ≥ E0.3 (–34%) > E0.1 Rate of patients with decrease in epidermal thickness @ 42 d: E1.0 (4/4 [100%]) ≥ E0.3 (8/12 [66.7%]) ≥ E0.6 (3/6 [50.0%]) Rate of patients with decrease in epidermal T cell infiltration @ 42 d: E1.0 (4/4 [100%]) ≥ E0.3 (8/12 [66.7%]) ≥ E0.6 (3/6 [50.0%]) Rate of patients with decrease in ICAM-1 expression @ 56 d: E1.0 (4/4 [100%]) ≥ E0.3 (8/12 [66.7%]) ≥ E0.6 (3/6 [50.0%]) Time to response (d): E (70)
Conclusions	Efalizumab may be effective in psoriasis

Box 6: Effects of efalizumab on quality of life in patients with psoriasis (26) [Prous Science CSline database].

Design	Multicenter, randomized, double-blind, placebo-controlled clinical study
Population	Patients with moderate to severe plaque psoriasis (n = 145)
Treatments	Efalizumab, 0.1 mg/kg i.v. infusion 1x/wk x 8 wks Efalizumab, 0.3 mg/kg i.v. infusion 1x/wk x 8 wks Placebo
Results	Dermatology Life Quality Index (score), change @ 56 d: E0.3 (–6.2) > P (–3.2) [$p = 0.026$] Rate of patients with “good” or “better” in Physician’s Global Assessment (%): E0.3 (48) > P (15) [$p = 0.0002$] PASI score, change: E0.3 >P [$p = 0.0001$]
Conclusions	Efalizumab 0.3 mg/kg improved quality of life in patients with plaque psoriasis

mean decrease in PASI scores was observed on day 42 in groups III, IV and V, respectively. A reduction in epidermal thickness, epidermal T-cell infiltration and ICAM-1 expression (on day 56) were detected in 8/12 group III patients, 3/6 group IV patients and 4/4 group V patients; CD11a in plaques was also found to be blocked and suppressed on peripheral blood mononuclear cells (PBMCs). PBMCs isolated from a patient in group IV on day 56

could not be activated by either OKT3 or phytohemagglutinin *in vitro*; responsiveness returned on day 70 (25) (Box 5).

hu1124 (0.1 or 3 mg/kg weekly i.v. infusion for 8 weeks) was also demonstrated to improve dermatologic-specific quality of life (QOL) according to results of a randomized, double-blind, placebo-controlled, dose-ranging study conducted in a total of 145 adult subjects with moderate to severe psoriasis (PASI 12 or greater with 10% or more of the body surface area affected). Although no significant differences in efficacy were noted between patients treated with the 0.1 mg/kg dose and placebo at the end of treatment, significantly more patients treated with 0.3 mg/kg achieved a Physician Global Assessment of good or better as compared to placebo (48 *vs.* 15%) and had significantly improved mean PASI scores. In addition, of the 98 patients completing QOL evaluations using the Dermatology Life Quality Index (DLQI) and the MOS-SF-36 Health Measure, those patients treated with 0.3 mg/kg (n = 52) displayed a significantly higher mean change in the DLQI score (–6.2 ± 5.5 *vs.* –3.2 ± 6.4) as compared to placebo (n = 30), indicating a significant improvement on day 56 from baseline (26) (Box 6).

An open-label, phase I/II trial demonstrating the safety and efficacy of hu1124 (0.7 mg/kg s.c. followed by 11 weekly injections of 1, 2 or 4 mg/kg) in 61 patients with moderate to severe plaque psoriasis (PASI ≥ 12; body surface area affected ≥ 15%). One week after the last dose, 61-88% of patients from all dose groups displayed a 50% or greater reduction in PASI scores. A decrease of 75% or more was observed in 30, 25 and 42% of the patients receiving the 1, 2 and 4 mg/kg doses, respectively. In addition, 25-50% of the patients from all dose groups had a score of excellent according to the Physicians Global Assessment. Treatment was well tolerated. No serious adverse events were seen. Minor flu-like symptoms were reported for the first and second dose (21, 22).

Investigation of the efficacy of hu1124 continues with 2 placebo-controlled phase III trials initiated in more than 1000 patients with moderate to severe plaque psoriasis and in an open-label trial examining the effects of a second course of hu1124 (0.7 mg/kg s.c. followed by 11 weekly doses of 1 or 2 mg/kg) in subjects with moderate to severe plaque psoriasis (PASI = 8-47; body surface area affected = 8-90%) who had already received the agent i.v. or s.c. in a previous phase I or II trial. Preliminary results from 50 patients participating in the open-label trial showed that 80% of the patients achieved similar or better PASI with the second treatment course as compared to the first course and 28 and 58% of the patients showed PASI reductions of 75 and 50% or better, respectively. Treatment was well tolerated with no serious adverse events observed. Those adverse events experienced were minor, with headache, rhinitis and other aches and pains the most common (27-29).

hu1124 is now in phase III trials for the treatment of moderate to severe plaque psoriasis and is also currently being evaluated as a treatment for organ transplant rejection. The safety and pharmacokinetics of the agent are under investigation in a 1-year phase I/II study involving kidney transplant patients (29).

Manufacturer

Genentech, Inc. (US) codeveloped with Xoma Ltd. (US).

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