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Dermatologic Drugs

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Abstract

This issue of **Drugs of the Future** features the *Annual Review of Dermatologic Drugs*. The following table lists 91 drugs under development in this area, including those drugs that have been published in previous issues of the journal and others in preparation for publication in the journal, as well as some drugs that have been launched for an indication other than that discussed in the review. Information on the following 10 products has been updated in this issue: alefacept, aminolevulinic acid, efalizumab, etanercept, imiquimod, leflunomide, maxacalcitol, paclitaxel, pimecrolimus and tacrolimus.

We would like to remind the readers that all of the information presented in this Review is available in electronic format in our drug discovery portal **Integrity**.

Annual Review 2002: Dermatologic Drugs

Drug	Source	Indication	Phase
ABX-IL-8	Abgenix	Psoriasis	II
AD-177	Arakis	Psoriasis	II
ADL-10-0101	Adolor	Dermal itch	II
AE-941[1]	Aeterna	Psoriasis	II
AGN-4310	Allergan/Ligand	Mucocutaneous toxicity	II
Alefacept[1]	Biogen	Psoriasis	Prereg
Alicaforsen[3]	Isis Pharmaceuticals	Psoriasis	II
Alitretinoin[2]	Basilea	Eczema	II
Aminolevulinic Acid Methyl Ester	Photocure	Actinic keratosis	L-2001
Aminolevulinic Acid[1,5]	Dusa Pharmaceuticals/Schering AG	Acne	II
		Warts	II
BAL-2299/Ro-65-2299	Basilea	Psoriasis	II
Bexarotene[2]	Ligand	Psoriasis	III
BI-K0376	Biosearch Italia	Acne	I
Bimosiamose	Texas Biotechnology	Psoriasis	I
BIRB-796	Boehringer-Ingelheim	Psoriasis	II
BMS-188667	Bristol-Myers Squibb/Novartis	Psoriasis	II
Chrysalin	Abbott/Chrysalis Biotechnology	Wound healing	II
Cipamfylline	Leo	Atopic dermatitis	II
Clobetasol Propionate[2]	Connetics	Psoriasis	III
CNI-1493	Cytokine PharmaSciences	Psoriasis	II
Daclizumab[2]	Protein Design Labs	Psoriasis	II
Daivobet	Leo	Psoriasis	L-2001
Dapsone[2]	Atrix Laboratories (formulation)	Acne	III
	Fujisawa	Acne	III
Dehydroepiandrosterone Sulfate	Pharmadigm	Wound healing	II
Denileukin Diftitox[2]	Ligand	Psoriasis	II
Desloratadine[1,2]	Schering-Plough	Chronic idiopathic urticaria	Reg-2001
Diltiazem[2]	Solvay/SLA Pharma	Wound healing	III
Dimericine	AGI Dermatics/Elan	Actinic keratosis	III
Doxercalciferol	Bone Care International	Psoriasis	I
DPC-168	Dupont Pharmaceuticals	Atinic keratosis	I
Dutasteride[1]	GlaxoSmithKline	Hair growth disorders	II
Eculizumab	Alexion	Psoriasis	II
		Dermatomyositis/Pemphigoid	I
Efalizumab[1]	Genentech/Xoma	Psoriasis	III
E-Matrix	Encelle	Wound healing	I
EO-1606	Leo	Atopic dermatitis	I
Epidex	Modex Therapeutics	Wound healing	II
Etanercept[1,2]	Immunex/Wyeth-Ayerst	Psoriasis	III
Ethinylestradiol/Chlormadinone Acetate[2]	Grünenthal	Acne	III
Fibrostat	Biovail/Procyon	Wound healing	II
Fluasterone	Hollis-Eden/Aeson Therapeutics	Actinic keratosis	II
Fluorouracil[2]	Dermik	Actinic keratosis	L-2001
HCT-1026[1]	NicOx	Psoriasis	II
		Atopic dermatitis	II
		Urticaria	I/II
HuMax-CD4	Genmab	Psoriasis	II
IC-747	Biogen/Icos	Psoriasis	I
IDEC-114	Idec/Mitsubishi Pharma	Psoriasis	II
IDEC-131	Idec	Psoriasis	II
Ilodecakin	Schering-Plough	Psoriasis	I
Imiquimod[1,2]	3M Pharmaceuticals	Actinic keratosis	III
Infliximab[2]	Centocor	Psoriasis	III
ISAtx-247	Isotechnika	Psoriasis	II
ISIS-104838	Isis Pharmaceuticals	Psoriasis	II
KB-261	Karo Bio	Skin atrophy	I
Leflunomide[1,2]	Aventis	Psoriasis	II
Levocetirizine	UCB	Chronic idiopathic urticaria	L-2001
Levonorgestrel/Ethinylestradiol	Wyeth Pharmaceuticals	Acne	Reg-2002

Continuation

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Drug	Source	Indication	Phase
Maxacalcitol[1,4]	Chugai	Psoriasis	L-2001
		Ichthyosis	L-2001
		Palmoplantar keratosis	L-2001
MBI-594AN	Micrologix	Acne	II
MDI-101	Molecular Design International	Acne	II
MDI-403	Molecular Design International	Acne	III
MDX-44	Medarex	Psoriasis	I/II
MV-9411	Miravant	Psoriasis	II
NO-Hydrocortisone	NicOx	Psoriasis	I
NV-07	Novogen	Sun damage	I
Olopatadine[1,2]	Kyowa Hakko	Urticaria/Psoriasis/Pruritus	L-2001
		Atopic dermatitis/Itching diseases	L-2001
Oprelvekin[2]	Genetics Institute/Wyeth Pharmaceuticals	Psoriasis	II
Orcell	Ortec	Wound healing	Reg-2001
Paclitaxel[1,2]	Angiotech Pharmaceuticals	Psoriasis	II
PEN-203	CoPharma	Psoriasis	II
PH-10	Photogen	Psoriasis	I
		Atopic dermatitis	I
Pimecrolimus[1]	Novartis	Psoriasis	II
		Atopic dermatitis	L-2002
Pimilprost[1]	Sumitomo	Wound healing	Prereg
Polyheal 1	Polyheal	Wound healing	I
Procyanidin B-2	Kyowa Hakko	Hair growth disorders	II
Psoraxine	Astralis/SkyPharma	Psoriasis	I
PVAC	Corixa/Medicis/Zenyaku Kogyo	Psoriasis	II
Repifermin	Human Genome Sci/GlaxoSmithKline	Wound healing	II
RN-1001/RN-1002	Renovo	Wound healing/Antiscarring	I
Siplizumab	MedImmune/Biotransplant	Psoriasis	II
Solarase	Quintiles/SkyePharma	Actinic keratosis	L-2001
SRL-172	SR Pharma	Atopic dermatitis	III
SRP-299	SR Pharma	Atopic dermatitis	I/II
Tacrolimus[1,2]	Fujisawa	Atopic dermatitis	II
TAK-427	Takeda	Atopic dermatitis	II
Trafermin	Kaken	Wound healing	Reg-2001
TRK-820	Daichi	Pruritus	II
TU-2100	Tamarkin/IBI	Acne	II/III
	Tamarkin	Psoriasis	II
		Seborrheic dermatitis	II
		Hair growth disorders	II
VAS-972	Vasogen	Psoriasis	II
Visiluzumab	Protein Design Labs	Psoriasis	II
Vitrix	Organogenesis	Wound healing	II
Zorcell	Immune Response	Psoriasis	II

[1]Previously published in Drugs of the Future. [2]Launched for another indication. [3]In preparation for Drugs of the Future. [4]Discontinued in the US and the UK. [5]Launched in 2000 for actinic keratosis.

Alefacept

The human LFA3/IgG1 fusion protein alefacept (Amevive™) is a disease-modifying agent that selectively targets a subset of T-cells – the memory-effector T-cells – that play a critical role in the pathogenesis of psoriasis.

Biogen simultaneously filed regulatory submissions in the U.S. and Europe last year seeking clearance to market alefacept for the treatment of moderate to severe chronic plaque psoriasis, and approval is anticipated by the end of 2002 or the first quarter of 2003. The company is also currently pursuing other indications for the fusion protein: pilot studies in scleroderma and rheumatoid arthritis have been initiated. Furthermore, Biogen expects to file for approval in other markets, including Canada and Australia, and is conducting phase I trials for registration in Japan (1-6).

The safety of multiple-dose i.v. alefacept (0.1, 2 or 40 mg/kg/week for 13 weeks) was demonstrated in a 3-month study conducted in baboons. The agent was well tolerated and no signs of toxicity, infectious compromise, neoplastic changes or death were observed. Treatment with alefacept resulted in dose-dependent reductions in peripheral and tissue lymphocyte counts; no T-cell subset was depleted even though high doses were administered. The decreases in CD2+ and CD4+ lymphocytes seen with doses of 2 and 40 mg/kg were similar and became saturated, with a plateau reached at about 80% below baseline. Peripheral lymphocyte counts returned to baseline by day 316 in the animals treated with the lowest dose; levels continued to recover at this time in animals treated with 2 and 40 mg/kg (7, 8).

The pharmacokinetics, tolerability and biological activity of alefacept (0.04 mg/kg i.m. or by 30-min i.v. infusion, or 0.15 mg/kg by i.v. bolus) were examined in 2 open-label, randomized, parallel-group studies in 38 healthy male volunteers. Alefacept was well tolerated; no serious adverse events were observed and no antibodies were detected. Common adverse events were headache, pharyngitis, rash and myalgia. Treatment resulted in reversible reductions in total lymphocytes and CD2, CD3, CD4, CD8 and CD19 subsets with a specificity for CD4 and CD8 memory-effector (CD45RO+) T-cells; lymphocyte counts were never reduced to levels below normal. Higher C_{max}, higher AUC and shorter t_{max} values were observed for i.v. as compared to i.m. administration. Following i.m. administration, serum concentrations of the agent increased dose-dependently and were detectable about 6 h postinjection; the apparent absorption $t_{1/2}$ was about 26 h. The relative bioavailability after i.m. administration was approximately 50%. The $t_{1/2}$ value for i.m. alefacept after completion of absorption was similar to that observed after i.v. administration (about 10 days). The pharmacokinetics for the i.v. bolus dose were consistent with those obtained after i.v. infusion (9).

Results from a multicenter, randomized, double-blind, placebo-controlled trial in patients with chronic plaque psoriasis showed that 12-week therapy with alefacept led to improvement and sustained clinical response in some patients and was well tolerated. In this study, 229 patients received weekly placebo or i.v. alefacept at 0.025, 0.075 or 0.150 mg/kg for 12 weeks. The Psoriasis Area and Severity Index (PASI) score, determined at baseline and at 2 weeks after the completion of therapy, showed a 21% mean reduction in the placebo group, as compared to decreases in the alefacept groups of 38% (0.025 mg/kg), 53% (0.075 mg/kg) and 53% (0.150 mg/kg). At 12 weeks after treatment, 28 patients in the alefacept group and 3 patients in the placebo group were clear or almost clear of psoriasis, although the patients in the placebo group showing improvement had received additional systemic psoriasis therapy. A significant correlation was found between changes in the PASI score and effect area under the curve values and CD8+ CD45RO+ and CD4+ CD45RO+ cells. Further analysis of the cohort receiving 0.075 mg/kg showed that those patients with the greatest decrease in CD8+ CD45RO+ (62%) or CD4+ CD45RO+ (45%) cells had the highest probability of achieving a 75% improvement in PASI, while patients with the smallest reduction in CD45RO+ cells had a decreased likelihood of reaching 75% PASI improvement. Similar results were observed in 62 other patients treated with alefacept as a 7.5-mg i.v. bolus/week for 12 weeks (10-15). The results of these and other studies that follow are summarized in Table I.

An open-label extension study of chronic intermittent therapy with alefacept 7.5 mg by i.v. bolus once weekly for 12 weeks followed phase II studies in patients with chronic plaque psoriasis. Treatment began when investigators determined that systemic therapy or phototherapy was required. Analysis of interim data suggested that alefacept treatment was safe and effective after both 1 and 2 courses of repeated therapy and no rebound phenomenon was reported during treatment or follow-up (16-18). A randomized, double-blind, placebo-controlled phase II study and an open-label phase II continuation study evaluated the safety of alefacept treatment in patients with moderate to severe chronic plaque psoriasis. The drug was administered as a 30-sec i.v. bolus or by i.m. injection over 12 weeks. The drug appeared to be well tolerated, with safety consistent over multiple courses (19).

The effect of alefacept on immune responses was evaluated by comparing T-cell humoral responses to phiX174 and to tetanus toxoid in psoriatic patients receiving alefacept 7.5 mg i.v. weekly or control. Alefacept targeted CD45RO+ T-cells but did not impair primary or secondary immune responses (20).

Researchers evaluated synovial T-cell and macrophage infiltration and the effect on skin lesions after

Table I: Clinical studies of alefacept (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Psoriasis	Randomized, double-blind, multicenter	Alefacept, 0.025 mg/kg iv over 30 s 1x/wk x 12 wk (n=57) Alefacept, 0.075 mg/kg iv over 30 s 1x/wk x 12 wk (n=55) Alefacent, 0.150 mg/kg iv over 30 s 1x/wk x 12 wk (n=58)	229	Alefacept was well tolerated and resulted in an improvement in chronic plaque psoriaris even after treatment cessation. The effect of alefacept on CD45RO+ cells was a predictor of safety, clinical response, remission and recurrence in chronic plaque psoriasis	10, 13
Psoriasis	Randomized, double-blind	Alefacept, 0.075 mg/kg/wk iv over 30 s x 12 wk		Alefacept produced disease clearing and long-lasting clinical remission in patients with psoriasis	11
Psoriasis	Randomized	Alefacept 0.075 mg/kg/wk iv over 30 s x 12 wk Placebo		Alefacept's effect on CD45RO+ cell subsets predicted clinical response in plaque psoriasis	12
Psoriasis	Randomized, double-blind	Alefacept, 7.5 mg iv bolus 1x/wk x 12 wk Placebo	11	Alefacept was well tolerated, with results showing a unique selectivity for memory-effector cells that might have the potential to provide a predictive, safe and efficacious treatment for psoriasis	14
Psoriasis	Open	Afelacept, 0.075 mg/kg/wk iv over 30 s x 12 wk (first course) if retreatment needed: 0.075 mg/kg/wk iv over 30 s x 12 wk (second course)		Alefacept was effective as a chronic intermittent therapy for patients with plaque psoriasis	16
Psoriasis	Randomized	Alefacept, 7.5 mg iv 1x/wk x 12 wk Control group (healthy volunteers)		Alefacept appeared to target pathogenic CD45+RO T cells without impairing primary or secondary immune response	20
Psoriasis, psoriatic arthropathy	Open	Alefacept, 7.5 mg iv 1x/wk x 12 wk	11	Alefacept was effective in improving joint scores and cutaneous signs and symptoms of psoriasis	21
Psoriasis, psoriatic arthropathy	Pooled data	Study I: (n=183) Alefacept, 7.5 mg iv bolus 1x/wk x12 wk x 2 courses Study II: Alefacept Study III: (n=11) Alefacept, 7.5 mg iv bolus 1x/wk x 12 wk		Alefacept was effective in reducing signs and symptoms and CD4+, CD8+ and CD68+ cell counts in psoriasis	22
Psoriasis	Randomized, multicenter	Study I: (n=553) Alefacept, 7.5 mg iv bolus 1x/wk x 12 wk Placebo Study II: (n=339) Alefacept, 10 mg im 1x/wk x 12 wk Alefacept, 15 mg im 1x/wk x 12 wk Placebo	892	Alefacept administered iv or im was well tolerated, did not induce immunogenic responses and was effective in reducing psoriasis symptoms	24

treatment of 11 patients with psoriatic arthritis with alefacept 7.5 mg i.v. for 12 weeks. Treatment resulted in improvements in clinical joint score and skin lesions which, in addition to changes in synovial tissue, indicated that memory-effector (CD45RO+) T-cells are involved in psoriasis and psoriatic arthritis (21, 22).

The results from phase III clinical trials of alefacept for the treatment of moderate to severe plaque psoriasis were positive and statistically significant. The double-blind, placebo-controlled studies involved more than 1100 patients, aged 16-84 years, with chronic plaque psoriasis that covered at least 10% of their total body surface area, at 100 sites in the U.S., Europe and Canada. The primary efficacy endpoint – a 75% or greater improvement in the PASI score 2 weeks after completion of a 12-week course of treatment – was achieved in both the i.m. and i.v. studies. Additional analyses showed that 71% of patients receiving 2 i.v. courses of alefacept therapy achieved a 50% or greater reduction in baseline PASI score and 40% achieved a 75% or greater reduction in baseline PASI score, compared to respective values at any time after the first i.v. dose of 56 and 28%; 57 and 33% of patients receiving i.m. drug achieved 50 and 75% reductions, respectively,

at any time after the first dose. Improvement measured by PASI score in the phase III trials correlated with reduction in CD45RO+ cells. Notably, in both studies, patients in the alefacept-treated groups achieved a statistically significant quality-of-life benefit, as measured by the Dermatology Life Quality Index. A 50% or greater reduction in baseline PASI score significantly correlated with improved quality of life. Alefacept was very well tolerated, was nonimmunogenic and was not associated with rebound (2, 23, 24).

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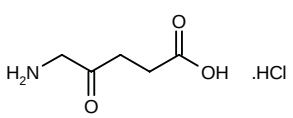
Aminolevulinic Acid Hydrochloride



Aminolevulinic acid is a photosensitive agent taken up preferentially in the diseased cells of precancerous lesions when applied to affected areas of the skin. When exposed to an appropriate light source, the agent is activated to destroy the cells via photodynamic therapy, with minimal damage to surrounding tissue.

Aminolevulinic acid-based PDT was introduced in 2000 in the U.S. as Levulan® Kerastick™ for the treatment of nonhyperkeratotic actinic keratoses of the face or scalp in conjunction with blue light illumination using the BLU-U Blue Light Photodynamic Therapy Illuminator. Developed and manufactured by Dusa and licensed worldwide, except for Canada, to Schering AG, the product is marketed in the U.S. by the Schering AG affiliate Berlex. Schering AG also filed the first European application for approval of Levulan® PDT in Austria in 2001 and has submitted filings in Brazil and Australia. Draxis Health, which holds exclusive Canadian rights to the product, received approval last year to market Levulan®

Table II: Clinical studies of aminolevulinic acid (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Acne, solar keratosis	Open	Aminolevulinic acid, 20% oil-water emulsion over 4 h + Polychromatic visible light, 13 J/cm^2	13	Photodynamic therapy (polychromatic visible light plus aminolevulinic acid) was effective in intractable acne	11
Solar keratosis	Randomized, double-blind, open, multicenter, pooled data	Aminolevulinic acid, 20% solution top + blue-light therapy (n=181) Placebo + blue-light therapy (n=62)	243	Topical aminolevulinic acid was safe and effective in multiple actinic keratoses of the face and scalp	12

Kerastick™ PDT in Canada for the treatment of actinic keratoses. Also under way are phase I/II trials of aminolevulinic acid PDT for the treatment of onychomycosis (nail fungus), plantar warts, acne and Barrett's esophagus. Dusa is also supporting a randomized, controlled clinical study taking place in England using aminolevulinic acid-based PDT following balloon angioplasty in the treatment of narrowed or blocked superficial femoral arteries. The aim of the trial is to confirm earlier positive pilot trial results and to determine whether adjunctive PDT treatment can prevent or reduce restenosis compared to the standard angioplasty-alone technique (1-7).

The efficacy of topical 5-aminolevulinic acid-based PDT and imiquimod (5% cream) as a treatment for multiple actinic keratoses was demonstrated in the case of a 75-year-old woman who suffered from the condition for 20 years. The skin of each forearm was treated with one of the therapies and both treatments resulted in good clinical response after 3 months of follow-up (8).

A study involving 4 patients with extensive scalp actinic keratosis demonstrated the efficacy of topical 5-aminolevulinic acid-based PDT. Three patients had clearing of lesions and 1 patient had significant improvement, with a duration of remission of 6 months (9).

The efficacy of PDT with topical 5-aminolevulinic acid (20%) for the treatment of skin cancers and precancerous lesions was demonstrated in a study in 72 male and female patients with superficial basal cell carcinomas, Bowen's disease lesions, squamous cell carcinoma, multiple solar keratoses or actinic porokeratoses of the legs. Lesions were exposed to 4-8 h of photoactivating light following topical application of the agent. From observations during follow-up (3 months to 5 years), it was concluded that 5-aminolevulinic acid-based PDT was effective as a treatment for superficial epithelial skin tumors, with excellent cosmetic results (10).

The efficacy of topical aminolevulinic acid (20% applied to lesions for 4 h with a light-shielding dressing)-based PDT as a treatment for intractable acne vulgaris was demonstrated in a study in 13 Japanese patients. Improvement in facial appearance and reductions in new lesions were observed at 1, 3 and 6 months posttherapy. Adverse events reported included discomfort, burning and stinging during irradiation, edematous erythema (3 days posttreatment), epidermal exfoliation (4-10 days posttreatment), irritation and hypersensitivity to physical stimulation (for 10 days after treatment) and pigmentation or erythema after exfoliation. Within 1 month, treated lesions returned to normal (11) (Table II).

Two multicenter, placebo-controlled (blinded and unblinded), randomized phase III studies conducted in 243 subjects with multiple actinic keratoses on the face and scalp examined the efficacy and safety of PDT with topical 5-aminolevulinic acid (20% solution). At 8 and 12 weeks posttreatment, 77 and 89% of patients, respectively, treated with 5-aminolevulinic acid-based PDT had a complete response. No significant treatment-related adverse events were observed. Burning or stinging at the treatment site during light exposure and transient post-therapy erythema and edema were the most common adverse events reported. Cosmetic response to treatment was rated excellent or good by 93% of the subjects and investigators rated cosmetic response good to excellent in 92% of the lesions treated (12) (Table II).

Multiple treatments with topical 5-aminolevulinic acid PDT were effective in a 70-year-old man with tumor-stage mycosis fungoides (13).

A self-adhesive matrix system containing crystalline aminolevulinic acid has been described. This application system is potentially useful for the photodynamic therapy and/or diagnosis of precancerous or cancerous skin lesions (14).

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Original monograph - Drugs Fut 1997, 22(1): 11.

Efalizumab

Efalizumab (hu1124, Xanelim™) is an immunomodulatory anti-CD11a recombinant humanized monoclonal antibody designed to inhibit the binding of T-cells to other cell types and target three key processes in the cascade of events leading to psoriasis: binding of T-cells through interactions with adhesion molecules on the endothelial cell surface, trafficking of T-cells into the skin and activation of T-cells.

Genentech and Xoma are jointly developing efalizumab for several indications, the first of which is moderate to severe chronic plaque psoriasis, for which phase III trials have been completed and U.S. and European regulatory filings are expected in the summer. Efalizumab is also in phase I/II clinical evaluation for use in kidney transplant rejection, and phase II trials in patients with rheumatoid arthritis are planned (1-8).

The pharmacodynamics of s.c. efalizumab were examined in two phase I trials, one of which also compared the pharmacokinetics of i.v. *versus* s.c. efalizumab. The data provided a clinical rationale for the s.c. administration of efalizumab, which is expected to increase patient compliance and improve outcomes (9). The results of this study and some of those that follow are summarized in Table III.

In a pharmacokinetic and pharmacodynamic study, patients with moderate to severe plaque psoriasis were initially administered s.c. efalizumab 0.7 mg/kg followed by 11 weekly injections of 1, 2 or 4 mg/kg. Subcutaneous administration resulted in decreased bioavailability compared to i.v. administration, although the pharmacodynamic parameters were similar. Circulating lymphocyte numbers increased approximately 2-fold and CD11a expression on T-cells was significantly reduced during the study. After drug clearance, these values returned to pretreatment levels (10).

Results from an open-label, multiple-dose trial involving subjects who had completed efalizumab treatment in prior phase I/II studies demonstrated the efficacy of efalizumab as retreatment (1 or 2 mg/kg/week s.c. for 12 weeks administered 14-139 weeks after the first treatment) for moderate to severe psoriasis. Concomitant UVB phototherapy or topical psoriatic therapy (excluding high-potency corticosteroids) was allowed, although systemic therapies were prohibited. Data from 50 patients showed that treatment with efalizumab resulted in comparable or lower Psoriasis Area and Severity Index (PASI) scores as compared to scores achieved after 12 weeks of initial therapy. A PASI improvement of 75 and 50% was seen in 28 and 58% of the subjects, respectively. Only mild to moderate adverse events were reported. Retreatment with efalizumab was well tolerated, with efficacy similar to the first treatment (11-13). An open-label, phase I/II trial assessed s.c. efalizumab as 12 weekly treatments in patients with moderate to severe plaque psoriasis. Doses began at 0.7 mg/kg and were increased to either 1, 2 or 4 mg/kg. Treatment was well tolerated and improved the signs and symptoms of the disease (14). A multicenter, double-blind, placebo-controlled phase II trial in 145 patients with moderate to severe plaque psoriasis assessed treatment with i.v. efalizumab (0.1 or 0.3 mg/kg) for 8 weeks. The treatment was well tolerated, with the higher dose producing greater clinical and histological improvement than the lower dose or placebo (15).

The preliminary 12-week results from a multicenter, randomized, open-label trial of efalizumab in patients with moderate to severe plaque psoriasis were presented earlier this year. The first treatment phase consisted of 12 weekly doses of s.c. efalizumab 2.0 mg/kg, with or without concomitant topical corticosteroid therapy with fluocinolone acetonide (Synalar® ointment 0.025%) applied during the last 4 weeks. A second phase will evaluate maintenance therapy with weekly s.c. efalizumub 1-2 mg/kg for an additional 48 weeks, and a third follow-up phase will be included. About 40% of patients achieved at least 75% improvement in the PASI score at 12 weeks, and addition of Synalar® did not increase the proportion of responders. Similar results were seen on secondary endpoints. Adverse events showed a similar incidence in the monotherapy and combination therapy groups, the most common being acute effects such as headache, infection, chills, pain, nausea, asthenia and fever (16).

Table III: Clinical studies of efalizumab (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Psoriasis	Open, multicenter	Efalizumab, 0.3 mg/kg sc (n=2 Efalizumab, 0.5 mg/kg sc 1x/wk x 8 wk (n=4) Efalizumab, 0.5 → 1.0 mg/kg sc 1x/wk x 8 wk (n=21) Efalizumab, 0.7 → 1.5 mg/kg sc 1x/wk x 8 wk (n=6) Efalizumab, 1.0 → 2.0 mg/kg sc 1x/wk x 8 wk (n=24)	57	Efalizumab was effective in chornic plaque psoriasis by reducing the expression of CD11a on circulating T cells, saturating T-cell surface and improving the PASI score	9
Psoriasis	Open	Efalizumab, 1 mg/kg sc 1x/wk x 12 wk Efalizumab, 2 mg/kg sc 1x/wk x 12 wk	50	Efalizumab retreatment efficacy was comparable to that of the first treatment and was well tolerated	11, 13
Psoriasis	Randomized, double-blind, multicenter	Efalizumab, 0.1 mg/kg iv over 90 min 1x/wk x 8 wk (=22) Efalizumab, 0.3 mg/kg iv over 90 min 1x/wk x 8 wk (n=75) Placebo (n=48)	145	Efalizumab antibody administered in weekly iv doses of 0.3 mg/kg over 8 weeks was well tolerated and improved chronic moderate to severe plaque psoriasis	15
Psoriasis	Randomized, open, multicenter	Efalizumab, 2 mg/kg sc 1x/wk x 12 wk (n=170) Efalizumab, 2 mg/kg sc 1x/wk x 12 wk + Fluocinolone acetonide, 0.025% ointment on wk 9-12 (n=169)	339	Efalizumab sc was safe, well tolerated and effective in improving signs of psoriasis in patients with moderate to severe plaque psoriasis. The addition of corticosteroid ointment did not improve the response	16
Psoriasis	Open, multicenter	Efalizumab, 1 mg/kg/wk sc (titrated from 0.7 mg/kg/wk) x 12 wk (n=20) Efalizumab, 2 mg/kg/wk sc (titrated from 0.7 mg/kg/wk) x 12 wk (n=20) Efalizumab, 4 mg/kg/wk sc (titrated from 0.7 mg/kg/wk) x 12 wk (n=21)	61	Weekly sc administration of efalizumab for 12 weeks was convenient, well tolerated and markedly improved moderate to severe plaque psoriasis	17, 18
Psoriasis	Randomized, double-blind, multicenter	Efalizumab, 1 mg/kg sc 1x/wk x 12 wk → (if ≤ 75% improvement in PASI) Efalizumab, 1 or 2 mg/kg sc 1x/wk or P x 12 wk (n=162) Efalizumab, 2 mg/kg sc 1x/wk x 12 wk → (if ≤ 75% improvement in PASI) Efalizumab, 1 or 2 mg/kg sc 1x/wk or P x 12 wk (n=166) Placebo → (if ≤ 75% improvement in PASI) Efalizumab, 1 or 2 mg/kg sc 1x/wk or P x 12 wk (n=170)	498	Efalizumab sc once weekly for 12 or 24 weeks was safe, well tolerated and improved quality of life, PASI and other parameters of psoriasis	21, 26, 27
Psoriasis	Randomized, double-blind, multicenter	Efalizumab, 1 mg/kg sc 1x/wk x 12 wk → (if ≥ 50% PASI improvement) Efalizumab, 2 mg/kg or P sc 1x/1-2 wk x 12 wk (n=232) Efalizumab, 2 mg/kg sc 1x/wk x 12 wk → (if ≥ 50% PASI improvement) Efalizumab, 2 mg/kg or P sc 1x/1-2 wk x 12 wk (n=243) Placebo x 12 wk → (if ≥ 50% PASI improvement) Efalizumab, 2 mg/kg or P sc 1x/1-2 wk x 12 wk (n=122)	597	Efalizumab treatment during 24 wks was safe, well tolerated and effective in improving lesions in chronic plaque psoriasis, with similar response when administered weekly or every other week	25, 28

The efficacy and safety of a 12-week course of s.c. efalizumab (1, 2 or 4 mg/kg/week) were examined in an open-label phase I/II study involving 61 subjects with moderate to severe psoriasis. Overall, 94, 75 and 31% of the patients had an improvement in PASI of at least 25, 50 and 75%, respectively. Improvement was observed early, with 32% of the subjects showing an improvement of at least 25% by day 14. The median times to achieve 25, 50 and 75% improvement were 21, 42 and 42 days, respectively. On day 84, the average reductions in the erythema, thickness and scaling components of PASI were 58, 55 and 59%, respectively, and pruritus (according to a 10-point subjective scale) was reduced from 5 to between 2 and 3 by day 84. Pharmacokinetic/pharmacodynamic analysis indicated that s.c. delivery was comparable to an i.v. formulation, and that the doses used provided drug levels sufficient to achieve reduced CD11a expression and binding site saturation. Good tolerance

was reported in most patients, the most frequent adverse events being headache, flu-like symptoms and psoriasis symptoms after completion of treatment (17, 18).

In two placebo-controlled phase III clinical trials in more than 1000 patients with moderate to severe plaque psoriasis, s.c. efalizumab was administered as an initial conditioning dose of 0.7 mg/kg in the first week, followed by weekly doses of 1.0 or 2.0 mg/kg. Pooled data demonstrated that almost 30% of efalizumab-treated patients had at least 75% improvement in the PASI score from baseline after 12 weeks of therapy. Improvement over placebo was seen after only 2-4 doses of efalizumab. Efalizumab-treated patients also had marked improvements in two other efficacy endpoints, showing decreases in plaque thickness and improvement in quality of life. Headache was the most frequent adverse event and acute events such as headache, fever, chills, nausea, vomiting and myalgia were seen mostly after the first two doses and decreased in incidence with subsequent doses to levels comparable to placebo (7, 19-23).

Initial results from the first of these 2 pivotal trials of efalizumab were presented at the Second Joint Meeting of the International Psoriasis Symposium and European Congress on Psoriasis held recently in San Francisco. In the 498-patient study, 39% of patients given 1 mg/kg and 27% of those given 2 mg/kg achieved the primary endpoint *versus* only 2% of placebo patients. Among 123 patients in both dose groups who received an additional 12 weeks of efalizumab after not achieving the primary endpoint during the initial treatment period, 20% more patients achieved at least 75% improvement in PASI score. In addition, 61% of patients on the lower dose of efalizumab and 51% of patients on the higher dose achieved PASI score improvement of 50% or greater after 12 weeks of treatment, *versus* only 15% of patients on placebo. Serious adverse events which may or may not be related to efalizumab included 1 case of tightness of the throat and another of reduced platelet counts. As an immunomodulatory agent, efalizumab may be associated with a potential risk of infection, but no increase in the rate of infection was seen in patients treated with efalizumab *versus* placebo in this study, and no T-cell depletion was detected (5).

The results from the second pivotal trial were presented at the American Academy of Dermatology Academy 2001 meeting in Anaheim, California. The study enrolled 597 patients between the ages of 18 and 75 years with moderate to severe plaque psoriasis covering at least 10% of total body surface area and a PASI score of 12 or higher. Results showed that 22 and 28% of patients administered 1 and 2 mg/kg, respectively, of efalizumab achieved a PASI score improvement of 75% or greater. Of the 134 partial responders, 58% (2 mg/kg weekly) and 29% (2 mg/kg every other week) achieved improvement of 75% or more in PASI score after 12 weeks. Furthermore, 12% of initial nonresponders administered the 4 mg/kg dose for an additional 12 weeks achieved scores of 75% or greater, and 52 and 57% of patients given 1 and 2 mg/kg of efalizumab, respectively, achieved over 50% improvement in PASI score (24). Findings presented at the 60th Annual American Academy of Dermatology meeting in New Orleans provided further evidence for early responses and improved response rates in some patients at 24 weeks compared to the first 12 weeks in these phase III clinical trials (8).

Data from phase III trials also indicated that semimonthly dosing with s.c. efalizumab (1.0 or 2.0 mg/kg) provides good maintenance therapy in responders, although partial responders required continued weekly administration (25). Treatment with efalizumab was also associated with significant improvements of almost 50% in the quality of life in these trials (26). Prolonging treatment from 12 to 24 weeks provided an improved response rate in terms of PASI scores (27, 28).

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Original monograph - Drugs Fut 2001, 26(3): 232.

Etanercept

Etanercept (Enbrel®), a biological response modifier marketed for the treatment of rheumatoid arthritis since 1998, was discovered and developed by Immunex and is marketed by Wyeth-Ayerst (now Wyeth Pharmaceuticals) and other Wyeth affiliates.

Etanercept was also recently approved by the FDA for use in psoriatic arthritis, an often painful chronic inflammatory disease characterized by joint and skin inflammation, alone or in conjunction with methotrexate. Immunex has also filed an sNDS in Canada seeking approval for etanercept for the same indication. Supporting the regulatory applications are results from phase II and III trials demonstrating greater improvement in signs and symptoms of both the joint and skin manifestations of the disease following treatment with etanercept than with placebo. Etanercept acts by binding to TNF and inhibiting the binding of TNF molecules to the receptor. Phase III studies are also under way in severe psoriasis and phase II studies in ankylosing spondylitis. Etanercept is also approved for the treatment of moderately to severely active polyarticular-course juvenile rheumatoid arthritis (JRA) in patients who have had an inadequate response to two or more disease-modifying medicines (1-3).

The FDA's approval of the sBLA was based on results from 2 multicenter, double-blind, randomized trials. In a 24-week phase III trial, patients were administered etanercept (25 mg s.c. twice weekly) and efficacy was measured by the number of subjects achieving the American College of Rheumatology preliminary criteria for improvement (ACR20). After 12 weeks of treatment, 59% of etanercept patients achieved an ACR20 response compared to only 15% of placebo patients; 38% of etanercept patients achieved an ACR50 response, compared to 4% of placebo patients, while 11% on etanercept achieved an ACR70 response, compared to 0% in the placebo group. Similar results were seen at week 24. In a subset of patients with a predefined severity of psoriasis, 47 and 23% of etanercept-treated patients achieved 50 and 70% improvement, respectively, in the Psoriasis Area and Severity Index (PASI), compared to 18 and 3%, respectively, in the placebo group. These results were similar to those seen in an earlier single-center, randomized, placebo-controlled study (3, 4).

The efficacy and safety of etanercept (25 mg s.c. twice weekly) as a treatment for chronic moderate to severe plaque psoriasis were demonstrated in a multicenter, randomized, double-blind, placebo-controlled, 24-week study involving 112 patients. Of the patients receiving etanercept, 30 and 56% experienced an improvement in PASI scores of 75% at 12 and 24 weeks, respectively; this contrasts with values of 2 and 5%, respectively, on placebo. Moreover, approximately 20% of patients administered etanercept for 6 months improved by 90% or more, whereas none of the patients in the placebo group showed this level of response. The incidence of adverse events was similar in both etanercept and vehicle groups (5, 6) (Table IV).

The results of a randomized, double-blind, placebo-controlled study in 205 patients with psoriatic arthritis showed that treatment with etanercept (25 mg s.c. twice weekly) significantly improved health-related

Table IV: Clinical studies of etanercept (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Psoriasis, psoriatic arthropathy	Randomized, double-blind, multicenter	Etanercept, 25 mg sc 2x/wk x 24 wk (n=57) Placebo (n=55)	102	Etanercept monotherapy was well tolerated and effective for the treatment of psoriasis	5
Psoriasis, psoriatic arthropathy	Randomized, double-blind	Etanercept, 25 mg sc 2x/wk x 24 wk (n=101) Placebo (n=104)	205	Etanercept was well tolerated and effective in improving the arthritis activity, psoriasis symptomatology, disability and health-related quality of life in patients with arthritis and psoriasis	7, 8
Psoriasis, psoriatic arthropathy	Randomized	Etanercept, 25 mg sc 2x/wk x 12 wk (n=30) Placebo (n=30)	60	Etanercept was safe, well tolerated and effective in improving signs and symptoms of psoriatic arthritis	9
Psoriasis	Open	Etanercept x 36 wk (n=19) Placebo x 12 wk → Etanercept x 24 wk (n=19)	38	Etanercept was well tolerated and effective in reducing symptoms of psoriasis	10

quality of life as compared to placebo. The group treated with etanercept showed significant improvements in the Health Assessment Questionnaire, the Medical Outcomes Short Form 36 (SF-36) and the EuroQoL Feeling Thermometer at 24 weeks compared to baseline. Standard measures of disease severity showed that etanercept treatment significantly improved psoriasis in these patients and was well tolerated (7, 8) (Table IV).

In a placebo-controlled trial, 60 patients with psoriatic arthritis were randomized to placebo or etanercept 25 mg s.c. twice weekly. Etanercept was well tolerated and resulted in significant improvements in arthritis symptoms and in psoriatic lesions (9).

A 24-week, open-label extension study has continued an initial 12-week evaluation of etanercept treatment in patients with psoriatic arthritis and psoriasis. In the extension study, the median PASI scores decreased from 5.5 to 3.2 in patients treated with etanercept in the initial study and from 6.8 to 2.1 in patients originally treated with placebo. Patients treated originally with etanercept showed continued improvement, and similar improvement was seen in patients originally given placebo once they started etanercept treatment. Eighteen psoriasis patients were taking methotrexate concomitantly at baseline, 56% of whom decreased the dose after the extension study and 39% of whom discontinued methotrexate altogether. At the end of the extension study, 82% of psoriatic arthritis patients had achieved the PsARC response criteria and 74% the ACR20 criteria (10) (Table IV).

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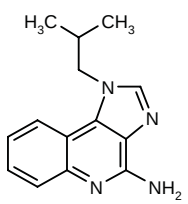
Original monograph - Drugs Fut 1998, 23(9): 951.

Imiquimod



Imiquimod (Aldara™) is the first in a new class of drugs called immune response modifiers (IRMs) which demonstrate both antitumor and antiviral activity *in vivo*. Imiquimod has been marketed as a 5% cream by 3M Pharmaceuticals for several years for the treatment of external genital and perianal warts/condyloma acuminata in adults.

When administered 2 days prior to UVB radiation, topical imiquimod prevented UVB-induced cutaneous immunosuppression in a mouse model of contact hypersensitivity. Contact hypersensitivity was inhibited by only 10% in imiquimod-treated animals as compared to control mice, indicating a suppression of UVB-induced immunosuppression. Imiquimod was not effective when applied after UVB treatment. Imiquimod may therefore be effective in preventing UVB-induced immunosuppression, which is involved in the development of skin cancer (1).

The possibility of using imiquimod to remove tattoos within the first 24-72 h of tattooing was investigated in 5 albino guinea pigs. Six hours after tattooing, guinea pigs received either no treatment (A), treatment with petrolatum (B), alternating treatment with tretinoin b.i.d. and imiquimod b.i.d (C), treatment with imiquimod q.i.d (D), or treatment with tretinoin q.i.d. (E). Treatment lasted 7 days and biopsies were taken at 6 h, 7 days and 29 days. While the tattoos in guinea pigs in groups A and B appeared normal, the tattoos of guinea pigs in group C were significantly faded. There was no evidence of tattoo dye in the skin of guinea pigs in group D and the tattoos of guinea pigs in group E were faded. It was concluded that imiquimod alone, and to some extent in combination with tretinoin, may be useful for the acute removal of tattoos (2).

Vaginally applied imiquimod was evaluated for its effects in a murine model of *Chlamydia trachomatis* genital tract infection. Female mice were treated with placebo or imiquimod (10 mcl of a 1:4 dilution in saline) as either a prophylactic starting 5 days before infection and continuing for 5 days, a single prophylactic dose 2 h before infection, or as therapy on days 4-14 of infection. Prophylactic treatment beginning 5 days before infection was the only regimen having an effect and significantly reduced the duration of infection (3).

The efficacy and safety of imiquimod (5% cream) as a treatment for several dermatoses, including genital and nongenital human papillomavirus warts, herpes simplex, vulvar intraepithelial neoplasia, molluscum contagiosum, actinic keratosis, basal and squamous cell carcinoma and Bowen's disease, were discussed in a recent report (4).

A double-blind, randomized, vehicle-controlled trial tested the efficacy and tolerability of imiquimod cream (5% 3 times weekly for up to 12 weeks) as a treatment for multiple actinic keratoses in 36 patients. Clinical clearance of lesions was seen in 84% of the patients and partial clearance in 8%. No improvements in size or number of lesions were observed in the vehicle-treated group. Imiquimod was well tolerated. Adverse events related to treatment were erythema, mild induration, vesicles and slight erosion; a few mild adverse reactions to the vehicle cream were seen. No recurrence was reported after 6 months in patients treated with imiquimod (5). The results of this study and many of those that follow are summarized in Table V.

The efficacy and safety of imiquimod cream (5% 3 times weekly for 12 weeks) as a treatment for extensive actinic keratoses were demonstrated in 4 organ transplant patients (1 kidney, 1 liver and 2 heart transplant recipients) also receiving immunosuppressive treatment. Clinical histological clearance of all lesions was seen in the liver and heart transplant recipients, with no scarring noted; the kidney transplant recipient experienced partial clearance. No systemic side effects were reported and no effects on systemic immunity or on the graft were detected. Mild application-site adverse events seen were erythema, edema and erosion (6).

Imiquimod was evaluated for efficacy and safety in 22 patients with actinic keratosis who applied the cream to one side of their body, and vehicle cream to the other side, 3 times weekly for 8 weeks or until clearance of lesions. Seventeen patients were evaluable for up to 8 weeks after treatment. Imiquimod-treated patients showed a significant reduction in the average number of lesions compared to placebo, with lesion counts remaining stable for up to 4 weeks posttreatment. Most patients reported acceptable mild to moderate adverse events, particularly irritation and reddening of the skin (7, 8).

The efficacy of topical 5-aminolevulinic acid-based photodynamic therapy and imiquimod (5% cream) as a treatment for multiple actinic keratoses was demonstrated in the case of a 75-year-old woman who suffered from the condition for 20 years. The skin of each forearm was treated with one of the therapies and both treatments resulted in good clinical response after 3 months of follow-up (9).

Fifty patients with actinic keratosis were treated with imiquimod over 6-10 weeks in a study with follow-up periods of up to 2 years. Patients were treated 3 times a week until all lesions developed a mild erythema, at which time therapy was reduced to 2 times a week. Imiquimod therapy cleared nearly all lesions, with no recurrences seen during the follow-up period. No histological signs of persisting lesions were detected. Mild erythema was observed in all patients, 2 of whom reported itching, but there were no signs of systemic effects. The activation of the local immune response by the drug was confirmed by comparison of gene expression in lesional biopsies taken before and during treatment (10).

The efficacy of imiquimod (5% cream 3 times weekly for 6-8 weeks) was demonstrated in a study in 6 men suffering from recurrent actinic keratosis for 5-16 years. All lesions were cleared by the end of treatment, with no histological indication of persistent actinic keratosis and no recurrences (11).

The safety and efficacy of imiquimod cream (5% twice weekly to scalp, face, arms and legs for 8 weeks initially, and then for 6 subsequent months) were examined in a randomized, placebo-controlled study in 12 subjects with actinic keratosis. Eleven patients completed the first 8 weeks, 10 of whom completed the following 6 months of treatment. A slight to marked improvement in lesions was observed in 64% of the patients after the first 8 weeks of imiquimod treatment. However, long-term, 6-month treatment with imiquimod did not afford added efficacy over placebo (4 of 5 imiquimod- and 4 of 5 placebo-treated patients were improved/cured after 6 months). Thus,

Table V: Clinical studies of imiquimod (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Solar keratosis	Randomized, double-blind, multicenter	Imiquimod, 5% cream 3x/wk x 12 wk or until lesions were resolved Placebo	25	Imiquimod 5% cream was well tolerated and effective in improving actinic keratosis lesions and preventing recurrence	5
Solar keratosis	Open	Imiquimod, 5% cream 3x/wk x 12 wk	4	Imiquimod 5% cream may be useful for the treatment of actinic keratosis lesions in organ transplant patients	6
Solar keratosis	Open	Imiquimod, 5% cream 3x/wk x 8 wk or until clearance Placebo (vehicle) applied on the other side of the body	22	Imiquimod 5% cream was safe and effective for the treatment of actinic keratosis	7
Hyperkeratosis, solar keratosis	Randomized, double-blind, crossover	Imiquimod, 5% cream top 3x/wk x 8 wk Placebo	17	Imiquimod 5% cream was effective in reducing actinic keratosis lesions	8
Hyperkeratosis, solar keratosis	Open	Imiquimod, 5% cream top 3x/wk x 6-10 wk	50	Imiquimod 5% cream was well tolerated and effective in actinic keratosis	10
Solar keratosis	Open	Imiquimod, 5% cream top bid x 6-8 wk	6	Imiquimod appeared to be a useful therapy for the treatment of actinic keratosis	11
Solar keratosis	Randomized	Imiquimod, 5% cream 2x/wk x 8 wk → Imiquimod, 5% cream 2x/wk x 6 mo Imiquimod, 5% cream 2x/wk x 8 wk → Placebo	12	Imiquimod 5% cream for 8 consecutive weeks was sufficient for improving actinic keratosis lesions	12
Basal cell carcinoma	Randomized, open, multicenter, pooled data	Imiquimod, 5% cream, 2-7 d/wk x 6 6-12 wk with or without site occlusion (n=257) Placebo (n=24)	281	Imiquimod 5% cream was acceptably safe and effective for the treatment of primary nodular basal cell carcinoma	16
Basal cell carcinoma	Open, mulicenter, pooled data	Imiquimod, 5% cream 2x/wk x 6 wk with treatment site occlusion Imiquimod, 5% cream 2x/wk x 6 wk without treatment site occlusion Imiquimod, 5% cream 3x/wk x 6 wk with treatment site occlusion Imiquimod, 5% cream 3x/wk x 6 wk without treatment site occlusion		Imiquimod 5% cream was effective in the treatment of basal cell carcinoma administered 2-3 times a week over 6 weeks	17
Keloid scar	Open	Imiquimod, 5 cream top od x 8 wk	12	Imiquimod 5% cream showed efficacy in reducing keloid recurrences after surgical excision	22
Venereal warts	Open	Imiquimod suppositories, 3x/wk x 3-4 mo	9	Imiquimod suppositories were safe, well tolerated and effective in the prevention of recurrences of widespread severe anorectal condyloma in male, HIV-negative subjects after surgical ablation	23
Alopecia areata	Open	Imiquimod, 5% cream top 1x/24-48 h x 18 wk-9 mo	5	Imiquimod was well tolerated and effective in the treatment of alopecia areata	24
Molluscum contagiosum	Open	Imiquimod, 5% cream top od (at night, washing the area(s) in the morning) x 4 wk	13	Imiquimod 5% cream shows activity and appears to be a safe treatment for molluscum contagiosum in children	29

short-term (4-8 weeks) treatment with the agent resulted in maximum responses in the treatment of actinic keratosis (12).

An almost 90% clearance of superficial basal cell carcinoma (sBCC) following daily application of imiquimod 5% cream for 6 weeks was reported. In this multicenter, dose-ranging phase II trial conducted in Australia and New Zealand, imiquimod cream was applied by 99 patients to a single biopsy-proven sBCC tumor for 6 weeks. Treatment efficacy was measured by complete histological clearance of sBCC at posttreatment biopsy. Of the 33 patients in the once-daily regimen, 87.9%

showed complete clearance of their sBCC tumor. Histological clearance rates were 100, 73.3 and 69.7% on twice-daily, twice-daily 3 times/week and once-daily 3 times/week regimens, respectively. Dose-related inflammatory skin reactions at the site of application were common but the treatment was generally well tolerated. Based on the results of this study, 3M decided to advance the product to phase III trials, which will include 48 sites in the U.S. and more than 75 international sites (13, 14).

Imiquimod 5% cream showed promise as a treatment for sBCC in 2 randomized, multicenter, dose-response trials. In the first study, patients received a single sBCC dose for 6 weeks (once daily, twice daily 3 days/week or once daily 3 days/week). In the second study, patients were treated with a single sBCC for 12 weeks (once daily, once daily 5 days/week or once daily 3 days/week). The histological tumor clearance rates for the 96 evaluable patients in the first study were 88, 73 and 70% for the once-daily, twice-daily 3 days/week and once-daily 3 days/week treatment groups, respectively. For the 118 evaluable patients in the second study, these rates were 87, 81, 52 and 19%, respectively, for the once-daily, once-daily 5 days/week, once-daily 3 days/week and combined vehicle dosing groups. The incidence of local skin reactions increased in both studies with increasing dosing frequency. Local reactions led to 1 patient discontinuing in the first study and 17 patients in the second study (15).

The results of 3 randomized studies involving a total of 257 patients with nodular BCC indicated that imiquimod may be an effective and safe treatment. Patients received imiquimod 5% cream 2 or 3 days a week with or without occlusion or once or twice daily for 3 or 7 days a week in two 6-week open-label studies, or 3 or 5 days a week or once or twice daily in a 12-week vehicle-controlled trial. The rates of complete histological tumor clearance for imiquimod-treated patients ranged from 42-76% as compared to 13% on vehicle. Response rates for daily dosing and 5 times weekly dosing for 12 weeks (76 and 70%, respectively) were significantly better as compared to vehicle. Mild to moderate local skin reactions seen more frequently when dose was increased were erythema, scabbing, erosion, edema, induration, ulceration and flaking. The most common application-site adverse events were itching, tenderness, pain, bleeding, burning and irritation. Systemic adverse events related to treatment were not common (16).

According to results of 2 phase II studies and an open-label study involving over 100 patients with sBCC tumors, treatment with imiquimod 5% cream may be effective and safe when applied daily, 5 days a week or 3 days a week with occlusion for 6-12 weeks (17).

Imiquimod 5% cream was applied 3 times a week in 2 patients with intraepidermal carcinoma. In the first patient, 2 lesions resolved with 17 weeks of treatment, and no erythema or treatment discomfort was reported. Eight months after the initial presentation, a biopsy of the chest revealed a scar with an increased number of blood vessels. The biopsy showed no evidence of carcinoma, and the patient had no recurrence at 15 months posttreatment. Treatment of a single lesion in the second patient was stopped at week 9 when erythema and small erosions were observed in the treatment area. Three weeks later, the lesion healed without sequelae and no recurrence was seen at 12-month follow-up (18).

A clinical trial was conducted to evaluate the efficacy of imiquimod on skin metastases in 6 patients with malignant melanoma AJCC III/IV. Epifocal imiquimod was applied 3 times a week for 1 month and patients were observed for 3 months. Treated lesions were completely resolved in 1 patient, and in 2 patients the disease was stabilized with intermittent reduction of tumor growth and local tumor control over 9 and 6 months, respectively. Disease progressed in the other 3 patients. Local skin irritation was the only therapy-related adverse event. Immunomonitoring studies detected the induction of cytotoxic T-cells specific for the melanoma antigens MelanA/MART1 and gp100, respectively, in 2 of 3 patients with clinical responses (19).

Imiquimod (5% cream 3 times weekly at night without occlusion for 6 weeks) was shown to be effective in treatment-resistant verrucae planae (affecting fingers, hands and lower arms) in a 42-year-old man. The patient suffered from the condition for more than 2 years and previous treatment with keratolytic agents, cryotherapy, cimetidine and dimepranolinosin had no long-term efficacy. After 6 weeks of treatment, warts were no longer visible. No adverse events were reported during treatment (20).

A 44-year-old male suffering from epidermodysplasia verruciformis since the age of 10 showed clearing of warts upon treatment with imiquimod (3 times weekly for 12 weeks) (21).

Imiquimod 5% cream has been investigated for its ability to induce natural interferons and limit the recurrence of keloids after surgical excision. Imiquimod 5% cream was applied directly to the suture line and the surrounding area after 13 keloids were surgically excised from 12 patients. Nightly applications limited to 125 mg of cream were applied for 8 weeks. Eight patients completed the treatment period and a minimum of 6 months of follow-up, with none of their excised keloids recurring. No systemic symptoms of interferon toxicity were observed and the degree of application-site adverse reactions was deemed acceptable. None of the 5 keloids of 4 other patients who completed treatment and 3-5 months of follow-up have recurred. Thus, imiquimod appears to be a safe and effective treatment for minimizing keloid recurrences (22).

The efficacy of imiquimod (5.2-mg suppositories) was shown in 9 HIV-negative males who had undergone surgical ablation of widespread, severe anorectal condyloma. Treatment was well tolerated, only 1 patient developing mild erythema with pain requiring interruption of treatment. All patients were disease-free at follow-up of 13 months (23).

The efficacy of topical imiquimod (5% cream once daily or every 2 days) in inducing hair regrowth was demonstrated in 5 patients with alopecia areata (4

females and 1 male). The girl showed regrowth of hair in two-thirds of the affected area after 6 weeks of treatment. Two women and the man also had regrowth by 6 weeks. All patients had regrowth at follow-up ranging from 18 weeks to 9 months. Treatment was well tolerated, with no serious adverse events observed. Once-daily treatment with the agent was associated with mild ulceration and erythema in the male, which was resolved when treatment was administered only every 2 days (24). Another study has been initiated to examine the efficacy of topical imiquimod (5% b.i.d.) as a treatment for alopecia areata (25).

Topical imiquimod (once daily in 2 cycles of 3 weeks) proved effective as a treatment for chronic discoid lupus erythematosus of the scalp in the case of a 58-year-old woman. The patient had been previously treated with topical steroids, hydroxychloroquine, dapsone, mycophenolate mofetil and methotrexate without success; systemic corticosteroids (methylprednisolone 16 mg/day) were able to control the condition. However, the patient experienced complete remission within 4 weeks after treatment with imiquimod (26).

The efficacy of topical imiquimod (5% cream) as a treatment for bowenoid papulosis was demonstrated in a 38-year-old woman presenting with genitoanal papular skin lesions. The patient had received previous treatments without success. However, with imiquimod treatment, the patient experienced complete clinical resolution within 8 weeks and no precancerous epidermal changes were seen at 1, 6 and 18 months after treatment (27).

Carbon dioxide laser excision combined with postoperative topical imiquimod treatment was shown to be effective in managing recurrent facial keloids in the case of a patient suffering from the condition for 15 years (28).

The safety of imiquimod (5% cream nightly for 4 weeks) as a treatment for molluscum contagiosum was demonstrated in a study involving 13 children (mean age = 7 years). Results from the 12 subjects who completed the study showed that the only adverse events were application-site reactions. No systemic toxicity was observed (29).

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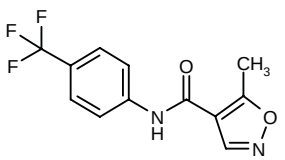
Leflunomide



Leflunomide, sold as Arava™, is currently available from Aventis as a disease-modifying antirheumatic drug (DMARD) for the treatment of active adult rheumatoid arthritis. Ongoing studies are evaluating its efficacy in other indications including psoriasis and psoriatic arthritis.

Six patients with psoriatic arthritis were given leflunomide as a loading dose of 100 mg on days 1-3 followed by 3 months of treatment at a dose of 20 mg. Preliminary results indicated that leflunomide was well tolerated and active in this indication (1) (Table VI).

A chart review of 12 patients who took part in an open clinical trial of leflunomide in recalcitrant psoriatic arthritis and psoriasis indicated that leflunomide can be an effective therapy for these conditions for up to 31 months (2) (Table VI).

Eotaxins are members of the CC family of chemokines and are suspected of being involved in the activation and accumulation of eosinophils in inflamed tissue, via binding to the CCR3 receptor, in eosinophil-mediated conditions such as bullous pemphigoid. As the DMARD leflunomide was recently reported to have beneficial effects in patients with bullous pemphigoid, the effects of leflunomide, its metabolite A-771726 and ciclosporin were examined on the production and release of eotaxin *in vitro*. Using human dermal fibroblasts stimulated with IL-4 and TNF-α, it was found that only A-771726 at concentrations of 50-200 mcmol was associated with significant (almost complete) suppression of eotaxin production. According to these findings, leflunomide and/or its metabolite may have potential in eosinophil/eotaxin-mediated disorders (3).

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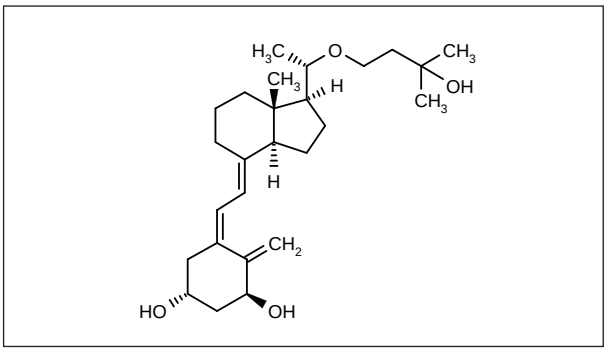
Table VI: Clinical studies of leflunomide (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Psoriasis, psoriatic arthropathy	Open	Leflunomide, 100 mg po od x 3d → 20 mg po od x 3 mo	6	According to these preliminary results, leflunomide was well tolerated and effective in psoriatic arthritis	1
Psoriasis, psoriatic arthropathy	Open	Leflunomide, 10-30 mg po od x 8-31 mo (mean 23 mo)	13	According to these results, leflunomide may be effective in psoriasis and in psoriatic arthritis	2

Maxacalcitol



The vitamin D derivative maxacalcitol was introduced in Japan as Oxarol® (ampoules for injection) by Chugai in 2000 for the treatment of secondary hyperparathyroidism in patients with chronic renal failure maintained on dialysis. Chugai and Maruho are also developing the drug as an ointment for the treatment of psoriasis. Maxacalcitol exerts its beneficial effects in psoriasis by inducing cell proliferation and differentiation in the skin (1, 2).

A stereoselective synthesis of maxacalcitol has been described using the Lythgoe-Hoffmann-La Roche convergent Wittig-Horner approach to condense the phosphine oxide (XIV) and ketone (XXIV):

Synthesis of phosphine oxide (XIV): Epoxidation of *l*-carvone (I) with H_2O_2 and LiOH in methanol gives the epoxide (II), which is reduced with L-Selectride in THF to yield the alcohol (III). Oxidation of the isopropenyl group of (III) with OsO_4, KIO_4, MCPBA and AcOH affords the acetate (IV), which is hydrolyzed to the diol (V) with MeONa in methanol. Protection of the two OH groups of (V) with TBDMS-Cl and imidazole provides the bis-silyl ether (VI), which is oxidized with periodic acid in ethyl ether to give the aldehyde (VII). Compound (VII) is submitted to a Wittig condensation with CBr_4, PPh_3 and Zn in dichloromethane to yield the dibromovinyl compound (VIII), which is converted into the acetylenic vinyl triflate (X) by treatment with LDA in THF followed by the triflic imide (IX). Cyclization of triflate (X) by means of $Pd(OAc)_2$ and PPh_3, followed by carbonylation with CO in methanol provides the methyl ester (XI) as a 2:1 mixture of the *Z*- and *E*-isomers. Photoisomerization of this mixture (XI) under the Hoffman-La Roche conditions (presence of 9-fluorenone) gives the *Z*-isomer (XII) in a high yield. Reduction of ester (XII) with DIBAL in toluene provides the primary alcohol (XIII), which is finally converted into the phosphine oxide (XIV) by known methods (3). Scheme 1.

Synthesis of ketone (XXIV): Reaction of the known diol (XV) – obtained by degradation of vitamin D_2 – with TsOH in pyridine gives, regioselectively, the monotosylate (XVI), which is protected at the secondary OH group by silylation with TBDMS-Cl and imidazole to yield the silyl ether (XVII). Oxidation of the tosyloxy group of (XVII) with O_2 and *t*-BuOK in DMSO/*t*-BuOH affords ketone (XVIII), which is reduced with K and *i*-PrOH providing alcohol (XIX). Condensation of compound (XIX) with ethyl propynoate (XX) by means of NMM in benzene gives the alkoxyacrylate (XXI), which is reduced with H_2 over Pd/C in ethanol to yield the alkoxypropionate (XXII) (4). Deprotection of the OH group of (XXII) with HF in acetonitrile affords alcohol (XXIII), which is oxidized with pyridinium dichromate (PDC) in dichloromethane providing ketone (XXIV). Wittig-Horner condensation of ketone (XXIV) with phosphine oxide (XIV) by means of BuLi in THF yields the corresponding adduct (XXV), which is submitted to a Grignard reaction with MeLi in THF to give the protected maxacalcitol precursor (XXVI). Finally, this compound is desilylated by means of tetrabutylammonium fluoride (TBAF) in THF (5). Scheme 2.

The efficacy of topical maxacalcitol (25 μg/g for 4 weeks) for the treatment of chronic psoriasis vulgaris was demonstrated in an open study involving 10 patients suffering from the condition. All patients experienced an improvement in psoriatic plaque with a significant decrease in the proportion of cells in the S and G_2/M phase, labeling and mitotic indices and percentage of Ki-67-positive cells compared to nontreated skin. In addition, treatment resulted in a normalization of the dermal expression of keratin 1, keratin 5, involucrin and loricrin (6).

Vitamin D derivatives, such as maxacalcitol, have been claimed to be useful for the treatment of excessive melanocyte proliferation and pigmentation (7).

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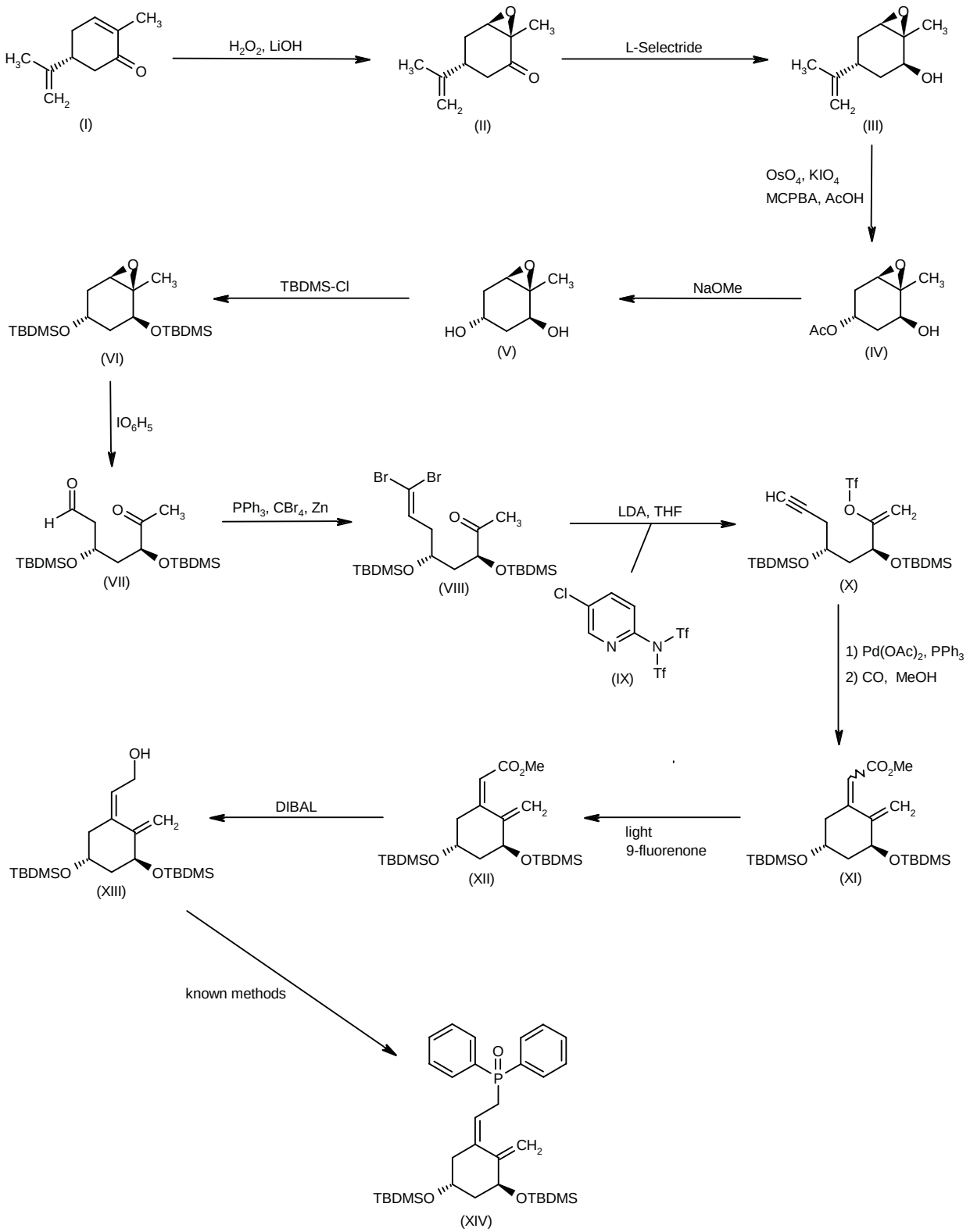
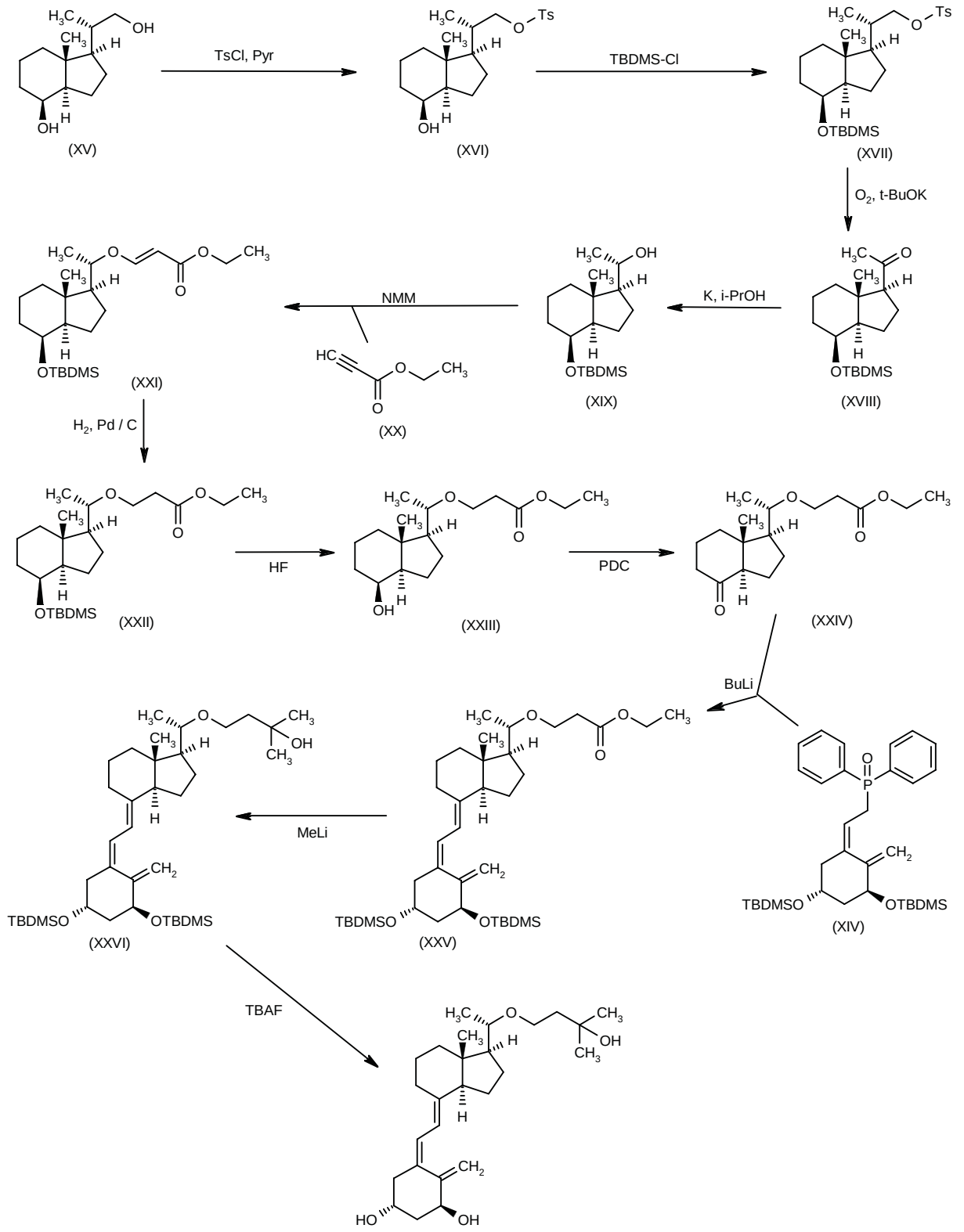
7. Nakayama, J. *Remedies for pigmentation and melanocyte proliferation inhibitors.* WO 0128565.

Original monograph - Drugs Fut 1996, 21(12): 1229.

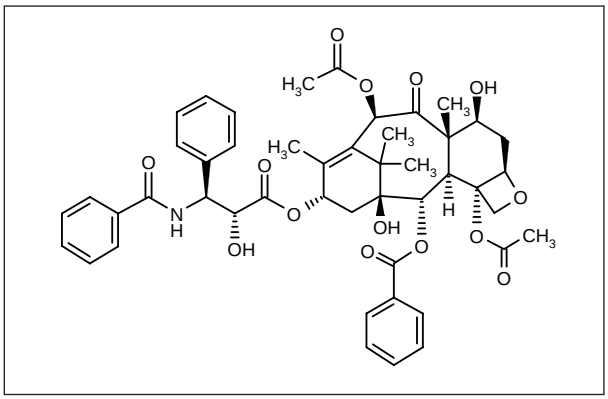
Scheme 1: Synthesis of Intermediate (XIV)



Scheme 2: Synthesis of Maxacalcitol



Paclitaxel



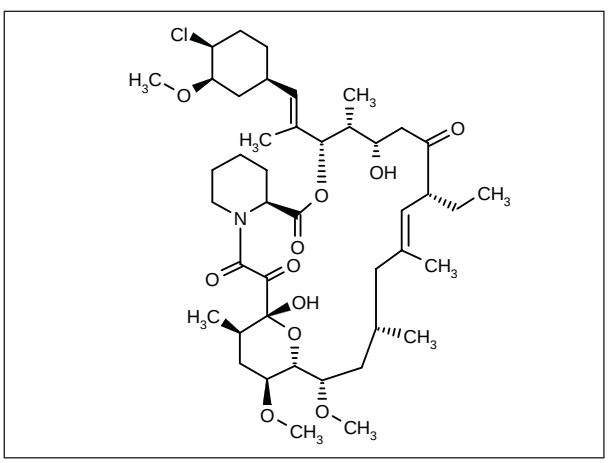
The widely used anticancer agent paclitaxel was first introduced under the name Taxol(R) almost a decade ago by Bristol-Myers Squibb. A number of companies are currently developing the drug in novel formulations and for various indications.

Encouraging results from a pilot phase II clinical study of micellar paclitaxel (Paxceed™) in the treatment of severe psoriasis have led Angiotech to extend the study to include up to 13 additional patients. Results have shown that the initial 5 patients who received monthly intravenous infusions over a 6-month period all experienced 50-75% improvement in the severity of the disease. Paxceed™ was also shown to be safe and well tolerated. Under the extension of the study, the intravenous infusions will be administered once every 2 weeks. As in the original study, patients must have had previous systemic treatment, but receive no other treatment during the study. The company is also developing Paxceed™ for secondary progressive multiple sclerosis, for which it is in phase II trials, and rheumatoid arthritis, for which it is in phase I studies (1).

1. *Angiotech extends study of micellar paclitaxel as treatment of severe psoriasis*. DailyDrugNews.com (Daily Essentials) Nov 21, 2001.

Original monograph - Drugs Fut 1986, 11(1): 45.

Pimecrolimus



Pimecrolimus (SDZ-ASM-981, Elidel®) is a skin-selective inflammatory cytokine inhibitor that works by selectively targeting T-cells in the skin, stopping them from producing the cytokines which cause the inflammation, redness and itching associated with atopic dermatitis, or eczema.

Pimecrolimus was discovered and developed by Novartis and was approved last December by the FDA as the first steroid-free prescription cream for the short-term and intermittent long-term treatment of mild to moderate atopic dermatitis in patients aged 2 years and older in whom conventional therapies are inadvisable. Now available in the U.S., it also received its first European approval – in Denmark – for the treatment of atopic dermatatis in patients as young as 3 months of age. Applications for marketing approval are also under consideration in Canada and Switzerland. Pimecrolimus is expected to be launched in Denmark in mid-2002, and regulatory rapprovals in the rest of Europe are set to follow under the mutual recognition procedure (1-3).

A review has been published discussing the preclinical development of pimecrolimus as a treatment for inflammatory skin diseases such as atopic dermatitis, allergic contact dermatitis (ACD), irritant contact dermatitis and plaque-type psoriatic dermatitis. Topical pimecrolimus was as effective as clobetasol-17-propionate without causing skin atrophy in a pig ACD model. The agent administered orally was superior to tacrolimus in mice and rat ACD models. Pimecrolimus also decreased skin inflammation and pruritus in an atopic dermatitis model involving hypomagnesemic hairless mice. Moreover, pimecrolimus was less active than tacrolimus in rat immunosuppressive models (4).

The safety of macrolide immunomodulators including tacrolimus and pimecrolimus was summarized in a recent review. The article discussed systemic and topical toxicities associated with the agents and concluded that the agents are very safe (5).

An *in vitro* study using an allogeneic mixed lymphocyte reaction in human monocyte-derived dendritic cells showed that pimecrolimus potently inhibited the induction

of coreceptors involved in dendritic cell-dependent activation of T-cells. Exposure to the agent resulted in concentration-dependent inhibition of CD25, CD54, CD134 and CD137 upregulation; 80% inhibition was seen at a concentration of 10 nM. Pimecrolimus was found to be 10-fold more potent that ciclosporin (6, 7).

Pimecrolimus was as effective as FK-506 (tacrolimus; ED_{50} = 48 mg/kg p.o.) and superior to ciclosporin (ED_{50} > 90 mg/kg p.o.) in a murine model of ACD. In a rat model of ACD, the lowest effective doses of pimecrolimus and ciclosporin were 12.5 and 50 mg/kg, respectively; FK-506 had no effect even at doses up to 25 mg/kg p.o. Following s.c. administration, pimecrolimus (ED_{50} = 20 mg/kg), FK-506 (ED_{50} = 0.3 mg/kg) and ciclosporin (ED_{50} = 2.5 mg/kg) showed dose-dependent effects in models of localized graft-versus-host reaction; ciclosporin and FK-506 were 8 and 66 times superior to pimecrolimus in this model. Studies using an allogeneic kidney transplant model showed that the lowest dose of pimecrolimus required to prolong survived to 100 days or more was 15 mg/kg, as compared to 5 mg/kg for ciclosporin and 1 mg/kg for FK-506. These results show that pimecrolimus is highly potent in skin inflammation models but less active in immunosuppression models, indicating the skin specificity of the agent (8-12).

Pimecrolimus (1% cream) was shown to be as effective as tacrolimus (0.1 and 0.03% cream) in a pig model of ACD. Moreover, sites treated with pimecrolimus were less greasy and sticky than those treated with tacrolimus (13).

An *in vitro* study using purified cutaneous mast cells or basophil-containing peripheral blood leukocytes from healthy human donors demonstrated that pimecrolimus (0.1 nmol/l to 1 μmol/l) markedly inhibited mediator release from mast cells and basophils (*i.e.*, anti-IgE-induced histamine release, calcium ionophore + phorbol myristate acetate-induced TNF release, tryptase release, LTC_4 release). The effects of pimecrolimus were greater than those observed with ciclosporin and dexamethasone (14).

A study has genomically analyzed blood cells from psoriatic patients treated with pimecrolimus (30 mg b.i.d. p.o.) and placebo involved in a 4-week trial. Blood samples were obtained 13-14 days posttreatment. Results showed that pimecrolimus treatment caused a downregulation of mRNA expression of genes associated with the macrolactam pathway and inflammation (*e.g.*, macrophilin-12, calmodulin, histone 2, histone 3.3, cyclin D2, leukotriene A4 hydrolase, prostaglandin endoperoxide synthase, LFA-1, P-selectin, L-selectin, RANTES, HLA class II). No alterations in genes associated with apoptosis, stress induction or enzymatic induction were observed with treatment (15-17).

Results of a randomized, double-blind study conducted in 16 healthy volunteers showed that topical pimecrolimus (1% cream b.i.d. 6 days/week for 4 weeks) applied to healthy forearm skin did not cause skin atrophy. Significantly less epidermal thinning was seen with pimecrolimus on day 29 as compared to betamethasone-17-valerate (0.1% cream) and triamcinolone acetonide (0.1% cream). The significant thinning of the skin observed with the corticosteroids started on day 8, in contrast to pimecrolimus which was not significantly different from the vehicle (18). The results of this study and many of those that follow are summarized in Table VII.

The safety and efficacy of pimecrolimus (1% cream b.i.d. for 6 weeks) for the treatment of infants (n=186; aged 3-23 months) with mild to moderate atopic eczema were demonstrated in a multicenter, randomized, 26-week study which included a 6-week, double-blind, vehicle-controlled phase followed by a 20-week open-label phase. A total of 89 and 52% of the pimecrolimus- and vehicle-treated patients, respectively, completed the double-blind phase, at which time significantly more pimecrolimus-treated patients had their atopic eczema cleared or almost cleared as compared to vehicle-treated patients (54.5% *vs*. 23.8%) according to Investigator's Global Assessment scores. The mean decrease in the Eczema Area and Severity Index (EASI) was significantly greater in the pimecrolimus as compared to the vehicle group (–61.78% *vs*. +7.35%). Significantly more pimecrolimus-treated patients had no or minimal pruritus as compared to vehicle-treated patients (72.4% *vs*. 33.3%). The agent was well tolerated, only 2.9% of the patients discontinuing due to adverse events (19-22).

The efficacy and safety of topical pimecrolimus (1% cream b.i.d. for 6 weeks) were examined in 2 multicenter, randomized, double-blind, vehicle-controlled studies conducted in 403 pediatric subjects (2-17 years of age) with mild to moderate atopic dermatitis. Subjects completing the 6-week double-blind phase were subsequently enrolled in a 20-week open-label phase examining efficacy on an as-needed basis. Significantly improved Investigator's Global Assessment (IGA) scores were observed in the pimecrolimus group as early as day 8. Mean reductions in EASI for the treated and vehicle groups were about 45 and 1%, respectively, and significantly more pimecrolimus-treated subjects were determined to be treatment successes at the end of the double-blind phase. Significantly more pimecrolimus-treated subjects had little or no pruritus as compared to the vehicle. Treatment was well tolerated, only about 3% of the subjects discontinuing due to adverse events. Of the pimecrolimus-treated subjects, only 10% as compared to 13% in the vehicle group reported burning at the application site. No systemic or serious adverse events were observed (20, 23).

The ability of pimecrolimus to improve the quality of life was also evaluated in these studies. Parent's Index of Quality of Life-Atopic Eczema (PIQoL-AE) scores were available from 241 cases at baseline and 193 cases at 6 weeks. Although both the pimecrolimus and vehicle groups showed significant improvement in PIQoL-AE at 6 weeks, the improvement was significantly greater with pimecrolimus (24). Rapid responses were observed in those patients who were switched to pimecrolimus from the vehicle in the open-label phase. Improvements were

Table VII: Clinical studies of pimecrolimus (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Psoriasis	Randomized, double-blind	Pimecrolimus, 30 mg po bid x 4 wk (n=7) Placebo (n=2)	9	Genomic analysis of patients with plaque psoriasis showed antiinflammatory activity associated with oral pimecrolimus treatment	17
Healthy volunteers	Randomized, double-blind, crossover	Pimecrolimus, 1% cream top bid x 6d/wk x 4 wk Betamethasone valerate, 0.1% cream top bid x 6d/wk x 4 wk	16	Pimecrolimus was devoid of atrophogenic properties	18
Allergic dermatitis infantile eczema	Randomized, double-blind, open, multicenter	Pimecrolimus, 1% cream top bid x 26 wk (n=122) Placebo x 6 wk → Pimecrolimus, 1% cream top bid x 20 wk (n=64)	186	Preliminary results indicate that pimecrolimus was safe and effective in improving signs and symptoms of atopic eczema in children 3-23 months of age after 6 weeks of treatment	19, 21, 22
Allergic dermatitis, infantile eczema	Randomized, double-blind, open, multicenter	Pimecrolimus, 1% cream bid x 26 wk (n=267) Placebo (vehicle) x 6 wk → Pimecrolimus, 1% cream bid x 20 wk (n=136)	403	Treatment with pimecrolimus cream 1% was safe and more effective than its corresponding vehicle in improving quality of life in children with atopic dermatitis, with improvement observed by the first week	23-25
Allergic dermatitis	Open multicenter	Pimecrolimus, 1% cream bid PRN x 1 y	11	Long-term topical pimecrolimus treatment on an as-needed basis for atopic dermatitis was well tolerated and resulted in consistently low blood drug concentrations in infants as young as 4 months of age	29
Allergic dermatitis	Open	Pimecrolimus, 1% cream bid PRN x 1 y	40	Long-term topical pimecrolimus treatment on an as-needed basis for atopic dermatitis was well tolerated and resulted in consistently low blood drug concentrations regardless of the extent of the lesions treated and the duration of therapy	30, 31
Allergic dermatitis	Open	Pimecrolimus, 1% cream bid x 3 wk	12	Pimecrolimus treatment twice daily for 3 weeks was safe and effective for the treatment of moderate to severe extensive atopic dermatitis	33
Allergic dermatitis	Open	Pimecrolimus, 1% cream bid x 3 wk	10	Pimecrolimus appeared to be effective for the treatment of atopic dermatitis in children	37
Allergic dermatitis	Randomized, double-blind, open, multicenter, pooled data	Study I: (n=316) Tacrolimus, 0.1% ointment top x 12 mo Study II: (n=328) Pimecrolimus, 1% cream top x 12 mo Triamcinolone acetonide, 0.1% cream top x 12 mo	644	Pimecrolimus cream was safe and as effective as tacrolimus ointment in atopic dermatitis,although the results have limitations due to differences in study designs	39
Allergic dermatitis	Pooled data	Pimecrolimus, 1% cream top bid Tacrolimus, 0.1% ointment top bid		Pimecrolimus and tacrolimus were safe and effective in atopic dermatitis in children	40
Allergic dermatitis, infantile eczema	Randomized, double-blind, multicenter	Pimecrolimus, 1% cream top bid x 12 mo + (if investigators' Global Assessment flares severity = 4-5) Corticosteroids, top (n=204) Standard care x 12 mo + (if Investigators' Global Assessment flares severity = 4-5) Corticosteroids, top (n=46)	251	Preliminary results at 6 months indicated that long-term treatment with pimecrolimus was safe and more effective than standard care in reducing the incidence of flares and the use of corticosteroids in children 3-23 months old with atopic eczema	41, 42

Continuation

Table VII (Cont.): Clinical studies of pimecrolimus (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Allergic dermatitis, infantile eczema	Randomized, double-blind, multicenter, pooled data	Pimecrolimus, 1% cream top bid x 6 mo (infants) or 6-12 mo (children) + (if Investigators' Global Assessment severity = 4-5) Corticosteroids, top Standard care x 12 mo + (if Investigators' Global Assessment severity = 4-5) Corticosteroids, top	964	Pimecrolimus was safe and more effective than standard care in reducing the incidence of flares and the use of topical corticosteroids in atopic eczema in children and infants without effects on the systemic immune response	43
Allergic dermatitis	Randomized, double-blind, multicenter	Pimecrolimus, 1% cream bid x 12 mo + (if flares not controlled) Corticosteroids, top (n=474) Placebo + (if flares not controlled) Corticosteroids, top (n=237)	711	Pimecrolimus was effective in reducing disease flares and the need for topical corticosteroids in children with atopic dermatitis	44
Allergic dermatitis, infantile eczema	Randomized, double-blind, multicenter	Pimecrolimus, 1% cream top bid x 12 mo + (if Investigators' Global Assessment flares severity = 4-5) Corticosteroids, top Standard care x 12 mo + (if Investigators' Global Assessment flares severity = 4-5) Corticosteroids, top	713	Long-term treatment with pimecrolimus was safe and more effective than standard care in reducing the incidence of flares and the use of topical corticosteroids in children with atopic eczema, without effects on the systemic immune response	46, 47
Allergic dermatitis	Randomized, double-blind, multicenter	Pimecrolimus, 1% cream bid x 24 wk (Prednicarbate, 0.25% cream bid x 7 d if flare not prevented) (n=96) Placebo x 23 wk (Prednicarbate, 0.25% cream bid x 7 d if flare not prevented) (n=96)	192	Long-term topical pimecrolimus treatment reduced flare incidence and dependence on corticosteroids in patients with atopic dermatitis	48
Psoriasis	Randomized, double-blind	Pimecrolimus, 5 mg po od x 4 wk (n=8) Pimecrolimus, 10 mg po od x 4 wk (n=8) Pimecrolimus, 20 mg po od x 4 wk (n=8) Pimecrolimus, 20 mg po bid x 4 wk (n=8) Pimecrolimus, 30 mg po bid x 4 wk (n=8) Placebo (vehicle) (n=10)	50	Oral pimecrolimus was safe, well tolerated and effective in patients with moderate to severe chronic plaque psoriasis	49
Allergic dermatitis	Randomized, double-blind, multicenter	Pimecrolimus, 1% cream x 3 wk Placebo (vehicle)	257	Pimecrolimus treatment showed a beneficial effect on the quality of life and work productivity of patients with mild to moderate chronic hand atopic dermatitis	50
Psoriasis	Randomized, double-blind	Pimecrolimus, 20 mg po od x 4 wk Pimecrolimus, 20 mg po bid x 4 wk Pimecrolimus, 30 mg po bid x 4 wk Placebo		Oral pimecrolimus appeared to be a selective treatment for psoriasis, with the 20- and 30-mg twice daily doses inducing a clinical remission accompanied by corresponding histopathological and immunomorphological reversal (by reducing CD3+, CD4+ and CD8+ lymphocyte counts) of psoriatic features to normal or almost normal phenotype. Doses lower than 20 mg bid also might be effective	53, 54
Psoriasis	Randomized, double-blind, multicenter	Pimecrolimus, 1% ointment top bid x 21 d Calcipotriol, 0.005% ointment top bid x 21 d Clobetasol propionate, 0.05% ointment top bid x 21 d Placebo	23	Pimecrolimus ointment without occlusion was safe and more effective than placebo but less effective than the active comparators	55
Allergic dermatitis	Randomized, double-blind, multicenter	Pimecrolimus, 0.05% cream bid x 3 wk (n=42) Pimecrolimus, 0.2% cream bid x 3 wk (n=46) Pimecrolimus, 0.6% cream bid x 3 wk (n=42) Pimecrolimus, 1% cream bid x 3 wk (n=45) Betamethasone dipropionate, 0.1% cream bid x 3 wk (n=42) Placebo (n=43)	260	Pimecrolimus 1% cream was safe and well tolerated and was the most effective concentration for the treatment of atopic dermatitis	58

maintained throughout the 6-month study, with no rebound flares or tachyphylaxis observed. No systemic adverse events were observed and the incidence of skin infection was low. Adverse events were mostly mild to moderate and were consistent with common childhood illnesses. Application-site reactions which resolved early were observed in 18.1% of the patients in the open-label phase. Only about 3% of the patients discontinued due to adverse events (25).

Results of 4 open-label pharmacokinetic studies involving 58 infants (3-23 months), children (2-4 years) and adolescents (8-14 years) with moderate to severe atopic dermatitis (affecting 10-92% of the body surface area) showed that treatment with topical pimecrolimus (1% cream b.i.d. for 3 weeks to over 1 year) resulted in consistently low blood concentrations (93% lower than 2 ng/ml and 60% below 0.5 ng/ml). The agent was well tolerated locally and systemically and no accumulation was observed (26-28). Treatment with pimecrolimus (1% cream initially b.i.d. followed by treatment on an as-needed basis) was shown to result in minimal systemic absorption according to analysis of 11 infants (4-30 months) with moderate to severe atopic dermatitis participating in 2 open-label, pharmacokinetic, 1-year extension studies. Pimecrolimus blood levels were low throughout the study regardless of the severity of lesions (< 0.1-1.94 ng/ml). Blood levels were similar to those obtained for older children (> 2-4 years) and adults. Treatment was well tolerated with no systemic adverse events reported (29).

The safety, systemic exposure and efficacy of pimecrolimus cream 1% in the long-term treatment of atopic dermatitis were determined in an open-label study in 40 adult patients with moderate to severe atopic dermatitis. Patients were treated as needed on an outpatient basis for 1 year. Safety and efficacy were evaluated and blood samples taken at 1, 3 and 6 weeks after beginning therapy and then every month for a year. The most frequent drug-related adverse events were a feeling of warmth and burning sensation at the site of application. Systemic exposure was found to be consistently low, with no evidence of accumulation or increase in blood concentrations. Compared to baseline, 60% of the patients had major improvements at the end of the study (30-32).

An open-label study in 12 patients with extensive atopic dermatitis evaluated the tolerability and pharmacokinetics of pimecrolimus cream 1% applied twice daily. Treatment for 3 weeks produced low blood concentrations of the drug and no accumulation (33, 34).

The pharmacokinetics of 1% pimecrolimus cream were determined in 13 patients with moderate to severe chronic hand dermatitis treated twice daily for 3 weeks. The entire skin area of both hands was treated and evening application was followed by overnight occlusion with vinyl gloves. Blood concentrations of the drug after 3 weeks of treatment were consistently low and the cream was well tolerated both locally and systemically (35, 36).

The systemic exposure to pimecrolimus (1% cream b.i.d. for 3 weeks) was measured from blood samples (days 4 and 22 of treatment and 1 week posttreatment) taken from 10 young children (aged 1-4 years) with atopic dermatitis (23-69% of the body surface affected) participating in an open trial. Of the 63 samples taken, pimecrolimus concentrations were < 0.5 ng/ml in 63% and the maximum concentration seen was 1.8 ng/ml. No accumulation was observed between days 4 and 22. Pimecrolimus did not control the dermatitis of 2 patients who experienced flare. However, the EASI score of the remaining patients was improved by 8-89% at 3 weeks (37).

Pooled analysis of 2 independent, multicenter, randomized, 6-week trials in children with mostly moderate atopic dermatitis demonstrated that pimecrolimus 1% cream was able to significantly improve the signs and symptoms of eczema, particularly in the head and neck regions, traditionally difficult-to-treat areas. As measured by the EASI, head and neck eczema in the pimecrolimus-treated patients improved by an average of over 40% by 8 days and by nearly 60% at the end of the studies, compared to a deterioration on vehicle at 8 days and no improvement on placebo cream at the end of the study. Overall, the results demonstrated the rapid effect of the drug, with 45% reporting complete or good control of eczema at the first visit at 8 days compared to only 20% of placebo-treated patients. Moreover, pimecrolimus significantly improved pruritus, almost 45% of patients reporting no or mild itching within the first week compared to 26% of placebo patients, and over 60% reporting no or mild itching by day 29, which was maintained over the duration of the studies. Pimecrolimus was well tolerated (38).

A retrospective study examined the results of a randomized, open-label trial (n=316) of 1% tacrolimus ointment and a randomized, double-blind trial (n=328) comparing 1% pimecrolimus cream and 0.1% triamcinolone cream for the treatment of moderate to severe atopic dermatitis. Treatment with tacrolimus or pimecrolimus demonstrated encouraging degrees of efficacy and safety (39).

Data from 7 studies with pimecrolimus and 3 studies with tacrolimus in pediatric patients with atopic dermatitis indicated that pimecrolimus cream 1% and tacrolimus ointment 0.03% and 0.1% had comparable safety and efficacy in patients between 2 and 17 years of age (40).

Multicenter, randomized, double-blind, vehicle-controlled, 1-year studies involving infants (3-23 months) with atopic dermatitis compared the safety and efficacy of pimecrolimus cream (with allowance for use of emollients and medium/high-potency corticosteroids for flares) to conventional treatment (control; emollients and reactive use of corticosteroids for flares). Moreover, topical corticosteroid use was approximately double in the control group compared to the pimecrolimus group. Treatment was administered twice daily to affected areas at the first signs/symptoms of the condition and until they resolved. The results at 6 months showed that pimecrolimus significantly decreased flare incidence as compared to the control group. Treatment with pimecrolimus was significantly

more effective than the control in all secondary efficacy assessments (Investigator's Global Assessment, EASI and pruritus assessment). Relief of pruritus was seen within the first week of pimecrolimus treatment. Safety profiles were comparable for the two groups (41-43).

A multicenter, randomized, double-blind, vehicle-controlled, 1-year study involving 713 children (2-17 years) with atopic dermatitis compared the safety and long-term efficacy of pimecrolimus cream (with allowance for use of emollients and moderately potent corticosteroids for flares) to conventional treatment (emollients and reactive use of corticosteroids for flares) for preventing progression to flares. Treatment was administered twice daily to affected areas at the first signs/symptoms of the condition and until they resolved. Pimecrolimus significantly decreased the incidence of flare at 6 and 12 months as compared to control. Of those patients receiving pimecrolimus, 60 and 51% completed 6 and 12 months, respectively, without flares as compared to only 35 and 28%, respectively, in the control group. Time to corticosteroid use was significantly longer in the group treated with pimecrolimus. Frequency of positive antigens in the recall antigen test and safety profiles were similar for both groups. It was concluded that pimecrolimus was significantly more effective than conventional therapy in decreasing the incidence of flare in children with atopic dermatitis (43-47).

Another multicenter, randomized, double-blind, vehicle-controlled, parallel-group, 24-week study was conducted in 192 patients to compare pimecrolimus with conventional treatment (emollients and corticosteroids) in the long-term management of moderate to severe adult atopic dermatitis. Patients applied either pimecrolimus or vehicle cream (controls) twice daily at the first signs/symptoms of atopic dermatitis; corticosteroids (prednicarbate 0.25% cream) were allowed for uncontrolled flares. Significantly fewer pimecrolimus-treated patients required use of corticosteroids (14.8% *vs*. 37.3%) and they had significantly fewer flares (1.2 *vs*. 2.6 flares) as compared to controls. Disease severity was also significantly decreased in the pimecrolimus groups at 24 weeks as compared to controls (mean EASI scores: –5.5 *vs*. –2). Significantly more pimecrolimus-treated patients had no or only mild pruritus as compared to controls (58.3% *vs*. 36.5%) (48).

A randomized, double-blind, placebo-controlled study conducted in 50 patients with moderate to severe chronic plaque psoriasis demonstrated the safety and efficacy of pimecrolimus (5, 10 or 20 once daily or 20 or 30 mg b.i.d.). The agent was well tolerated and no serious adverse events were observed. The most common adverse event was a transient mild to moderate feeling of warmth seen in 1, 1, 3 and 7 patients treated with 5 mg once daily, 20 mg once daily, 20 mg b.i.d. and 30 mg b.i.d., respectively. No changes in blood pressure, serum creatinine, ECG, laboratory tests, glomerular filtration rate or renal function tests were seen. Only 1 patient had elevated glycemia after a glucose load during dosing. Doses of 20 and 30 mg b.i.d. resulted in median decreases in PASI score on day 28 of 60 and 75%, respectively, as compared to 4% on placebo (49).

Results from a 3-week, randomized, double-blind study followed by a 23-week open-label phase involving 257 patients with mild to moderate chronic hand dermatitis showed that there was no significant difference between pimecrolimus (1% cream) and the vehicle in total scores of the Dermatology Life Quality Index (DLQI) from baseline to week 22 or 26. However, the pimecrolimus-treated group tended to have a greater improvement in work impairment according to the Work Productivity and Activity Impairment Questionnaire (WPAI). Significant improvements in patient-reported quality of life, DLQI work and school scores and WPAI work impairment were obtained for the pimecrolimus groups over the vehicle when suspected etiology and/or surface involvement were controlled for (50, 51).

Three randomized, double-blind, vehicle-controlled phase III trials evaluated pimecrolimus as maintenance treatment during 12 months in infants, children and adults with mild to severe atopic dermatitis. Patients applied emollients for dry skin and either pimecrolimus cream or vehicle cream twice daily at the first sign of atopic dermatitis until resolution. Corticosteroids were used to treat disease flares. At 6 and 12 months, significantly fewer flares were seen in the pimecrolimus *versus* vehicle group in all 3 studies (52).

A double-blind study examined skin biopsies from patients with moderate to severe plaque psoriasis who were involved in a 4-week trial during which they received pimecrolimus (20 or 30 mg b.i.d. or 20 mg once daily) or placebo. Patients treated with pimecrolimus at doses of 20 and 30 mg b.i.d. exhibited 60 and 75% reductions in the PASI score, but the dose of 20 mg once daily was not effective. Analysis of skin biopsies showed that all doses of pimecrolimus significantly reduced CD3+ lymphocytes. The group receiving 30 mg b.i.d. showed a significant decrease in CD4+ lymphocytes. When treatment groups were pooled, CD8+ lymphocytes were significantly reduced. No effects on CD1+ Langerhans cells were observed. Treatment with 30 mg almost completely reversed disease phenotype, as determined by measuring Ki67+ KC, keratin 16, involucrin, HLA-DR, ICAM-1, CD31 and epidermis thickness. A reduction in proliferating blood vessels in the papillary dermis was also observed (53, 54).

Twenty-three inpatients with plaque-type psoriasis were entered in a randomized, double-blind, vehicle- and positive-controlled study comparing the efficacy of topical pimecrolimus (1% ointment b.i.d. for 21 days) with calcipotriol (0.005%) and clobetasol-17-propionate (0.05%) applied to psoriatic plaques without occlusion twice daily for 21 days. Pimecrolimus was significantly more effective than the vehicle according to the Total Sign Score2, *i.e.*, sum of erythema, induration and scaling scores (50% improvement *vs*. 28.6% with vehicle). However, both calcipotriol (71.4%) and clobetasol (87.5%) were more effective than pimecrolimus (55).

Results from a multicenter, randomized, vehicle-controlled study conducted in 183 infants aged 3-23 months with atopic dermatitis showed the efficacy and safety of pimecrolimus (1% cream b.i.d. for up to 6 weeks). Results from the first 83 patients showed that more treatment successes were seen on pimecrolimus (62.7%) as compared to vehicle (16.7%). Effects were rapid, with a significant difference seen by day 15 (47.5% *vs*. 16.7%). A significantly greater mean reduction in the EASI score was observed for pimecrolimus-treated patients as compared to vehicle and significantly more subjects treated with the agent had little or no pruritus early during treatment. Treatment was well tolerated and no serious or systemic adverse events were seen. Two patients from each group displayed adverse events at the application site (56).

A recent review discussed the clinical development of pimecrolimus (1% cream) as a treatment for inflammatory skin diseases including psoriasis, irritant contact dermatitis and allergic contact dermatitis. The efficacy and safety of the agent have been demonstrated in studies involving diverse patient populations. Three studies involving a total of 589 pediatric patients with atopic dermatitis reported significant and rapid improvements in the signs and symptoms of the condition with treatment. A 1-year study demonstrated the efficacy of the agent when applied at the first signs of eczema in preventing the progression of atopic dermatitis to flares in over 50% of the patients; treatment eliminated or reduced the need for topical corticosteroids. The agent also proved effective against chronic irritant hand dermatitis and chronic hand dermatitis of mixed causes (57).

A randomized, double-blind, dose-finding study of pimecrolimus cream (0.05, 0.2, 0.6 and 1%) was conducted in 260 patients with atopic dermatitis treated twice daily for up to 3 weeks. The 1% concentration of the cream was selected for development in phase III studies based on its safety, tolerability and superior efficacy in this study (58).

New phase III data announced at the recent American Academy of Dermatology meeting in New Orleans underline the efficacy and safety of pimecrolimus cream 1% as a new treatment option for atopic dermatitis. Results from 2 studies demonstrated that treatment with pimecrolimus is more effective than conventional treatment in reducing the incidence of disease flares, as well as the use of corticosteroids. One presentation of a 12-month, multicenter, double-bind study in 713 pediatric patients compared long-term treatment with pimecrolimus and a current conventional therapy regimen. Topical corticosteroids of mid-potency were used by both treatment groups to treat any severe flares. Results of this study showed that pimecrolimus significantly reduced the incidence of flares at both 6 and 12 months compared to conventional therapy. Pimecrolimus also demonstrated a steroid-sparing effect: 57% of patients in the pimecrolimus group had no flares that required treatment with a topical corticosteroid, as compared to 32% in the control group. A separate presentation of a 12-month, multicenter, double-blind study of similar design assessed the long-term safety and efficacy of pimecrolimus in 251 infants. The data at 6 months showed that 70% of the pimecrolimus-treated infants had no disease flare requiring treatment with a topical corticosteroid, as compared to 33% in the conventional treatment group. In addition to data reinforcing the safety and efficacy of pimecrolimus, new data were presented that demonstrated the overall tolerability of the treatment, most significantly the low incidence of application-site burning. Burning at the application site was measured through an extensive program that included controlled long-term (12-month) pediatric studies, controlled short-term (6-week) pediatric studies and uncontrolled long-term (20-week) pediatric extension studies. A total of 1226 pediatric patients were treated with pimecrolimus and 482 pediatric patients were treated in control groups (vehicle alone or intermittently with second-line corticosteroid to treat severe flares). The incidence of application-site burning with pimecrolimus was low and less than in vehicle-treated patients in the short-term studies (7.4% *vs*. 9.5%) and equivalent to vehicle in the long-term studies (7.4% for both) (59, 60).

Synergistic combinations containing a squalene epoxidase inhibitor and an immunosuppressant have been claimed for the treatment of fungal infections, particularly atopic and seborrheic dermatitis. A preferred combination comprises terbinafine hydrochloride and pimecrolimus (61).

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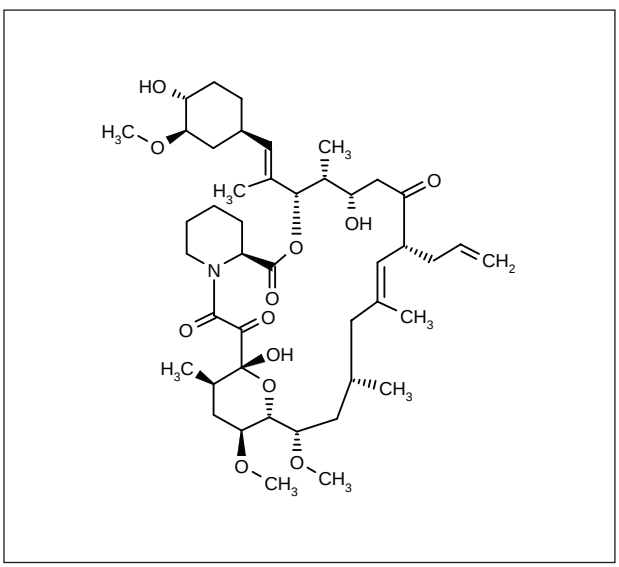
Tacrolimus



Fujisawa's tacrolimus ointment (Protopic®) is the first in a new class of agents known as topical immunomodulators (TIMs) that act selectively through a nonsteroidal pathway. It targets the immunological imbalance of the skin associated with atopic dermatitis, restoring the skin's normal function and preventing the release of inflammatory mediators and cytokines. The lack of side effects typical of conventional therapy with topical corticosteroids makes tacrolimus ointment suitable for treating sensitive or hard-to-treat skin areas such as the face and neck, in addition to the body and limbs.

Protopic® has been available in Japan for the treatment of moderate to severe atopic dermatitis since November 1999, and it was launched in U.S., Canada and Korea in 2001 and in Switzerland in January 2002.

The product was just recently approved by the European Commission for marketing in the E.U. countries, Norway and Iceland, and applications for the use of tacrolimus ointment in atopic dermatitis have also been submitted in Taiwan and China (1-4).

A review has been published discussing the nonclinical pharmacology and toxicology of tacrolimus (5). The safety of macrolide immunomodulators including tacrolimus and pimecrolimus was summarized in another recent review. The article discussed systemic and topical toxicities associated with the agents and concluded that they are very safe (6). The clinical development of topical tacrolimus in the treatment of atopic dermatitis and other skin conditions such as hand dermatitis, contact dermatitis, eyelid dermatitis, erosive lichen planus, steroid-induced rosacea, pyoderma gangrenosum and graft-versus-host disease has also been reviewed. Tacrolimus clinical trials have involved 12,000 patients and efficacy and safety profiles for the agent are available for up to 3 years of treatment (7). The preclinical and early clinical development of tacrolimus ointment as a treatment for atopic dermatitis was described in another review. Preclinical animal studies have shown that repeated administration of the agent for up to 1 year did not result in any significant macroscopic or microscopic dermal or systemic changes as compared to the vehicle. The safety and efficacy of the agent have also been demonstrated in phase II and III studies in patients with atopic dermatitis. Common side effects related to treatment were transient application-site burning sensation and pruritus (8).

Data from 7 studies with pimecrolimus and 3 studies with tacrolimus in pediatric patients with atopic dermatitis indicated that pimecrolimus cream 1% and tacrolimus ointment 0.03% and 0.1% had comparable safety and efficacy in patients between 2 and 17 years of age (9). Results of this study and many of those that follow are summarized in Table VIII.

A multicenter, noncomparative study investigated *Staphylococcus aureus* skin colonization in 19 adult patients with moderate to severe atopic dermatitis who were treated with tacrolimus 0.1% ointment twice daily for up to 1 year. *S. aureus* colonization was greatly reduced after only 1 week of treatment (10).

In 19 atopic dermatitis patients with recalcitrant facial erythema resistant to tacrolimus ointment, treatment with an original tacrolimus lotion for 6 months greatly or moderately improved symptoms in 89% of patients. Contact sensitivity to white petrolatum may have been responsible for the lack of response to tacrolimus ointment (11, 12).

Results from 12-week, double-blind, vehicle-controlled trials (1 pediatric and 2 adult trials) and 1 open-label, long-term (1-year) pediatric study conducted in a total of 1238 patients with atopic dermatitis showed that facial application of tacrolimus (0.03 and 0.1%) was safe and effective. Of all the patients participating in the 3 controlled trials, 86% presented lesions of atopic dermatitis on the head and neck and the efficacy of tacrolimus on these areas was similar to results obtained for overall body sites. Adverse event incidence ratios of facial to nonfacial site application were 0.9 for both formulations. Like other body sites, the most common adverse event on the face was skin burning, which resolved within the first days of treatment (13). Further analysis of these results indicated that treatment with tacrolimus generally did not increase the incidence of cutaneous infections (*e.g.*, skin infection, fungal dermatitis, herpes simplex, warts). However, significantly more patients treated with 0.03 and 0.1% tacrolimus developed folliculitis (4.7 and 3%, respectively, *vs.* 0.3% on vehicle) (14).

The safety and efficacy of tacrolimus ointment (0.03 and 0.1%) were demonstrated in a randomized, double-blind, vehicle-controlled, 12-week study in 351 children (2-15 years) with moderate to severe (61.5% of the patients) atopic dermatitis (mean percent body surface area affected of 47.7%). A clinical improvement of 90% or more was observed in significantly more tacrolimus-treated patients as compared to those given vehicle. Significant improvements in the signs and symptoms of atopic dermatitis, the percent body surface area affected and patient assessment of pruritus were observed early with tacrolimus and were maintained throughout the 12 weeks. A significantly higher incidence of skin burning sensation, pruritus, varicella and vesiculobullous rash was seen in patients treated with 0.03% tacrolimus; the incidence of adverse advents was similar in the 0.1% tacrolimus and vehicle groups. Tacrolimus was concluded to be safe for younger (2-6 years) and older (7-15 years) children (15, 16).

The efficacy of tacrolimus ointment (0.03 and 0.1% b.i.d.) was demonstrated in 2 randomized, double-blind, vehicle-controlled, 12-week studies involving 632 adults with moderate to severe (56% of the patients) atopic dermatitis (mean percent body surface area [BSA] affected of 45%). According to physician's global evaluation of clinical response, %BSA affected, individual signs of atopic dermatitis, the Eczema Area and Severity Index (EASI) score and patient assessment of pruritus, a significant improvement of 90% or more in disease status was observed in 27.5 and 36.8% of the patients in the 0.03 and 0.1% tacrolimus groups, respectively, as compared to 6.6% in the vehicle group. A 50% improvement was observed in 61.6 and 72.7%, respectively, of tacrolimus patients as compared to 19.8% in the vehicle group. A significantly greater improvement was observed for the tacrolimus-treated patients as compared to vehicle for all efficacy parameters. The 0.1% formulation was found to be more effective in patients with severe disease and/or extensive BSA involvement and in African Americans. The most common adverse events reported were skin burning sensation, pruritus, flu-like symptoms, skin erythema and headache; a significantly higher incidence of skin burning sensation, flu-like symptoms and headache were seen in the tacrolimus groups as compared to vehicle. More patients in the vehicle-treated group discontinued due to adverse events as compared to tacrolimus-treated groups. No changes in laboratory parameters were seen nor was tacrolimus detected in 80% of the blood samples analyzed (16-19).

Table VIII: Clinical studies of tacrolimus (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Allergic dermatitis	Pooled data	Pimecrolimus, 1% cream top bid Tacrolimus, 0,1% ointment top bid		Tacrolimus and pimecrolimus were safe and effective in atopic dermatitis in children	9
Allergic dermatitis	Open	Tacrolimus, 0.1% ointment bid x 1 y	28	Tacrolimus was effective in atopic dermatitis by reducing *S. aureus* colonization and improving eczema	10
Dermatitis	Open	Tacrolimus, 0.03% lotion top bid x 6 mo	19	Tacrolimus lotion was effective in recalcitrant facial atopic dermatitis in adults resistant to treatment with tacrolimus ointment	11, 12
Allergic dermatitis	Randomized, double-blind, pooled data	Tacrolimus, 0.03% x 12 wk (n=328) Tacrolimus, 0.1% x 12 wk (n=327) Placebo x 12 wk (n=328)	983	Both tacrolimus ointment concentrations were safe and effective for the treatment of atopic dermatitis regardless of race, although black adults can experience additional benefit from the 0.1% concentration. Moreover, it induced a low rate of cutaneous infections, with the exception of folliculitis and the response on the face was comparable to that observed on other body sites. The ratio of application site reaction in facial to nonfacial sites was 0.9	13,14,17
Dermatitis	Randomized, double-blind, multicenter	Tacrolimus, 0.1% ointment top bid x 12 wk (n=118) Tacrolimus, 0.03% ointment top bid x 12 wk (n=117) Placebo (vehicle) (n=116)	351	Tacrolimus ointment was safe and effective in atopic dermatitis in children	15
Allergic dermatitis	Randomized, double-blind, multicenter, pooled data	Tacrolimus, 0.03% ointment bid x 12 wk (n=58) Tacrolimus, 0.1% ointment bid x 12 wk (n=49) Placebo (n=34)	141	Both 0.93% and 0.1% tacrolimus ointment were safe and effective for the treatment of atopic dermatitis patients with limited disease	16
Allergic dermatitis	Randomized, double-blind, multicenter	Tacrolimus, 0.1% ointment top bid x 12 wk/until 1 wk after lesion clearing (n=209) Tacrolimus, 0.03% ointment top bid x 12 wk/until 1 wk after lesion clearing (n=210) Placebo (n= 212)	631	Tacrolimus ointment was well tolerated and effective in improving quality of life in adults, children and infants with atopic dermatitis	18, 19, 27
Eyelid dermatitis	Open	Tacrolimus, 0.1% ointment top bid x 8 wk	20	Topical tacrolimus ointment 0.1% was safe and effective in patients with moderate to severe eyelid dermatitis	21
Allergic dermatitis	Open, multicenter	Tacrolimus, 0.1% ointment top bid until 1 wk after lesion clearing	407	Tacrolimus ointment 0.1% monotherapy was safe with no increased risk for any adverse event and no signs of immunosuppressive effect in long-term treatment of atopic dermatitis	22, 23
Allergic dermatitis	Open, multicenter	Tacrolimus, 0.03% ointment top bid until 1 wk after lesion clearing Tacrolimus, 0.1% ointment top bid until 1 wk after lesion clearing	2582	Tacrolimus ointment 0.03% and 0.1% were safe with no increased risk for any adverse event and no signs of immunosuppressive effect in long-term treatment of atopic dermatitis	24
Allergic dermatitis	Open, multicenter	Tacrolimus, 0.1% ointment top bid until 1 wk after lesion clearing x 2 y	389	Tacrolimus ointment 0.1% was safe and did not increase the adverse events rate; there were no signs of immunosuppresive effects in long-term treatment of atopic dermatitis children	25

Continuation

Table VIII (Cont.): Clinical studies of tacrolimus (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Allergic dermatitis	Open, multicenter	Tacrolimus, 0.03-0.1% ointment top bid until 1 wk after lesion clearing	1941	Tacrolimus ointment was safe in children with atopic dermatitis	26
Allergic dermatitis	Open, multicenter	Tacrolimus ointment		The incidence of non-melanoma skin cancer in patients with atopic dermatitis may be higher than in the general population, although this might be related to prior therapy	28
Dermatitis	Open, multicenter	Tacrolimus, 0.1% ointment top bid until 1 wk after lesion clearing	255	Tacrolimus ointment 0.1% was safe and effective for the long-term treatment of atopic dermatitis in children	29
Allergic dermatitis	Randomized, double-blind, open, multicenter	Study I: (n=316) Tacrolimus, 0.1% ointment top x 12 mo Study II: (n=328) Pimecrolimus, 1% cream top x 12 mo Triamcinolone acetonide, 0.1% cream top x 12 mo	644	Tacrolimus ointment was safe and as effective as pimecrolimus cream in atopic dermatitis, although the results have limitations caused by differences is study designs	31
Dermatitis	Open, multicenter	Tacrolimus, 0.1% ointment top od or bid x 2 wk	47	Tacrolimus ointment 0.01% following corticosteroid discontinuation background therapy was safe and effective in refractory facial atopic dermatitis	32
Lichen planus	Open, retrospective	Tacrolimus, 0.03% ointment bid or tid (n=6) Tacrolimus, 0.1% ointment bid or tid or qid (n=4) Tacrolimus, 0.3% ointment bid or tid (n=3)	13	Tacrolimus ointment 0.1% was well tolerated and effective for the treatment of recalcitrant erosive or ulcerative oral lichen planus	35
Psoriasis	Open	Tacrolimus, 0.1% ointment top bid x 8 wk	20	Topical tacrolimus ointment was safe and effective in patients with psoriasis on the face and intertriginous areas	36
Vitiligo	Open, multicenter	Tacrolimus, 0.03% ointment top bid x 3-6 mo (n=4) Tacrolimus, 0.1% ointment top bid x 3-6 mo (n=1)	5	Topical tacrolimus ointment appeared to be a potential option for the treatment of vitiligo	37
Vitiligo	Open	Tacrolimus, 0.1% ointment top bid	5	Topical tacrolimus ointment 0.1% treatment for vitiligo resulted in at least partial repigmentation	38
Lichen planus	Open	Tacrolimus, 0.1% ointment bid x 8 wk or until asymptomatic	19	Tacrolimus ointment 0.1% was effective for the treatment of recalcitrant erosive or ulcerative oral lichen planus	39

The safety and efficacy of tacrolimus as a treatment for eyelid dermatitis was demonstrated in a study in which patients were treated b.i.d. for up to 8 weeks. No significant increases in intraocular pressure were seen and no patients developed cataracts or glaucoma during the study period. Local burning and itching after the first few applications were the only adverse events reported (20, 21).

An open-label study in 407 adults with atopic dermatitis treated with tacrolimus 0.1% cream applied twice daily for up to 3 years found the treatment to be safe. The incidence of adverse events, such as flu-like symptoms and skin infections, did not increase with long-term use of tacrolimus. The most common adverse events related to treatment were skin burning (30%), pruritus (29%) and erythema (14%). The most common infections were flu-like symptoms (23%), skin infection (13%) and sinusitis (8%) (22. 23). Interim safety analysis of tacrolimus ointment (0.1 and 0.03% b.i.d.) as a treatment for adult atopic dermatitis was performed using data from 2 multicenter, long-term extension and open-label studies involving a total of 8778 patents (16 years or older). A total of 2582 patients were evaluable. The median duration of follow-up was 2 years for 49% of the patients (n=407) in the extension study and 89 days for 2175 patients in the open-label study. No safety concerns were reported and safety profiles were similar to previous studies. The most common treatment-related adverse events were skin burning (30 and 23%), pruritus (29 and 20%) and skin erythema (14 and 9%) in the extension and

open-label studies, respectively. No immunosuppressive effects were seen (24).

The long-term (up to 3 years) safety of tacrolimus ointment (0.1% b.i.d. until 1 week after clearing) as a treatment for moderate or severe atopic dermatitis in pediatric patients (n=389; aged 2-15 years) was shown in a multicenter, open-label, noncomparative extension study. Of these patients, 234 completed a 2-year follow-up and 56 completed 3 years. The most common adverse events related to treatment were mild skin burning (18%), pruritus (15%) and skin erythema (5%); the incidence of these adverse events decreased within a few days of treatment. The most common infections were flu-like symptoms (37%), skin infection (18%), fever (17%) and pharyngitis (16%). The cases of herpes simplex infection seen (1.8%) occurred between 0 and 6 months, with no cases reported between 25 and 30 months. No local or systemic immunosuppressive effects were reported (25).

In an open-label, multicenter study, 7978 pediatric patients with atopic dermatitis were treated with 0.03 or 0.1% tacrolimus ointment applied to affected areas twice daily, continuing for 1 week if clearing occurred. The adverse event profile indicated that the treatment was safe in this patient population (26).

Analysis of results from 3 multicenter, double-blind, 12-week phase III studies including 985 patients with atopic dermatitis showed that tacrolimus ointment (0.03 and 0.1%) significantly improved health-related quality of life as compared to vehicle control groups in adults (16 years and older), children (5-15 years) and toddlers (2-4 years) (27).

Results from a 3-year follow-up of over 9500 patients with atopic dermatitis treated with tacrolimus ointment in 2 long-term safety trials showed that tacrolimus was not associated with an increase in nonmelanoma skin cancers (28).

The long-term efficacy and safety of tacrolimus ointment (0.1% b.i.d. for up to 1 year) as a treatment for pediatric atopic dermatitis were demonstrated in an open-label, noncomparative study in 255 children (2-15 years) with moderate to severe atopic dermatitis. Patients were treated for an average of 279 days. Improvements in the signs and symptoms of the condition, percent body surface area affected and patient or parent assessment of pruritus were seen within the first week of treatment and were sustained throughout the study period. The most common adverse events were application-site burning sensation and itching, which decreased after the first days of treatment (29).

A 52-week study in patients with atopic dermatitis indicated that tacrolimus ointment was cost-effective as compared to high-potency topical steroids (30).

A retrospective study examined the results of a randomized, open-label trial (n=316) of 1% tacrolimus ointment and a randomized, double-blind trial (n=328) comparing 1% pimecrolimus cream and 0.1% triamcinolone cream for the treatment of moderate to severe atopic dermatitis. Treatment with tacrolimus and pimecrolimus demonstrated encouraging efficacy and safety (31).

Tacrolimus 0.1% ointment was studied in 47 patients with severe facial atopic dermatitis refractory to corticosteroid treatment. Tacrolimus was found to be safe and effective in these patients, with improvements in the severity index and pruritus score (32).

A 35-year-old man with chronic actinic dermatitis was treated with 0.1% tacrolimus ointment applied twice daily to affected areas. After 2 months of treatment, there was a marked reduction in pruritus and the number and size of skin lesions (33).

A 34-year-old female patient with pustular psoriasis and a 71-year-old female patient with psoriasis vulgaris were treated with topical tacrolimus twice daily (< 10 g/day). Treatment was effective, with no renal dysfunction and marked reductions in the PASI score in both cases (34).

A retrospective analysis of 13 patients with symptomatic oral lichen planus demonstrated the efficacy of topical tacrolimus (0.03, 0.1 or 0.3% b.i.d., t.i.d. or q.i.d. for up to 1 year). Symptomatic responses (*i.e.*, lesion clearance) were reported in 11 patients (2 patients had no response), of whom 8 had a partial response and 3 had a complete response. Of those patients who responded, 7 had no flares with continued treatment and 4 had flares after stopping treatment. Adverse events (burning irritation and sore throat) were seen in only 3 patients and were mild (35).

The safety and efficacy of tacrolimus ointment (0.1% b.i.d. for 8 weeks) as a treatment for psoriasis on the face and/or intertriginous areas were demonstrated in an open-label study in 8 patients. Improvements in erythema, infiltration and desquamation were seen within 1 week and increased with treatment (36).

Tacrolimus ointment proved effective as a treatment for vitiligo in 5 patients, with at least partial repigmentation in all patients. Adverse effects consisted of burning and stinging at the application site in the first week of treatment (37, 38).

Results of an open-label, noncomparative study in 19 patients with biopsy-proven oral lichen planus (refractory to or dependent on immunosuppressive agents) indicated that topical tacrolimus (0.1% applied to oral lesions for 8 weeks) is effective. Significant improvement was observed within 1 week of treatment. By the end of treatment, a mean reduction of 73.3% in the area of ulceration was seen with therapy in the 17 patients who completed the study. The most common adverse effect was local irritation, seen in 6 patients. Following discontinuation of tacrolimus, 13 patients experienced a relapse within 2-15 weeks posttherapy (39).

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