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# Annual Update 2003 Dermatologic Drugs

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## Abstract

The Annual Update 2003 of Dermatologic Drugs is comprised of a Compendium of drug R&D in the area of dermatological disorders, including 91 drugs for the treatment of psoriasis, atopic dermatitis, miscellaneous eczema, acne, actinic keratosis, wounds, urticaria, pruritus, cutaneous atrophy, photodamage, wrinkling, ichthyosis, palmoplantar keratosis and hair growth abnormalities. The section on monograph updates offers updated information on the following dermatologic drugs that have been published in previous issues of the journal: adalimumab AE-941, alefacept, efalizumab, etanercept, imiquimod, pimecrolimus, pimilprost, siplizumab and tazarotene. The Annual Update also features a comprehensive table listing the drugs, their manufacturers, indications and developmental phases.

## Introduction

This month's Annual Update features a Compendium of drug R&D in the area of dermatological disorders. As can be seen in the following table, 91 drugs are under development for dermatological conditions, including psoriasis, dermatitis, acne, actinic keratosis, wounds, urticaria, pruritus, *etc*. The monograph update section offers updated information on the following dermatologic drugs that have been published in previous issues of the journal: adalimumab, AE-911, alefacept, efalizumab, etanercept, imiquimod, pimecrolimus, pimilprost, siplizumab and tazarotene.

According to IMS Health Drug Monitor, worldwide sales of drugs for dermatological disorders to purchasers and retail pharmacies totaled USD 8,535 in the 12-month period from November 2001 to November 2002.

## Annual Update 2003: Dermatologic Drugs

| Drug | Source | Condition | Phase |
|---|---|---|---|
| AA-10006 | Arachnova | Dermatitis, atopic | II |
| rAAT | Arrriva Pharmaceuticals/ProMetic Life Sciences | Dermatitis, atopic | I |
| Adalimumab[1,2] | Abbott | Psoriasis | II/III |
| AE-941[2] | AEterna | Psoriasis | I/II |
| AGN-194310 | Allergan | Acne | II |
| | Allergan | Dermatitis, atopic | II |
| | Allergan | Eczema | III |
| | Allergan | Psoriasis | III |
| Alefacept[2] | Biogen | Psoriasis | L-2003 |
| Alesse | Wyeth | Acne | L-2002 |
| Alicaforsen Sodium[2] | Isis Pharmaceuticals | Psoriasis | II |
| Alitretinoin[1] | Basilea Pharmaceutica | Eczema | II |
| Allox | IsoTis | Ulcer, skin | II |
| Aminolevulinic Acid Methyl Ester | Photocure | Keratosis, actinic | L-2001 |
| Aminolevulinic Acid[2,3] | Dusa Pharmaceuticals | Acne | I/II |
| AS-601811 | Serono | Acne | I |
| AVAC | Genesis Research and Development/SR Pharma | Dermatitis, atopic | I |
| BAL-2299 | Basilea | Psoriasis | II |
| Bexarotene[1] | Ligand | Dermatitis, hand | II |
| | Ligand | Psoriasis | II |
| BI-K0376 | Biosearch Italia | Acne | I |
| Bimosiamose | Revotar Biopharmaceuticals | Dermatitis, atopic | I |
| | Revotar Biopharmaceuticals | Psoriasis | I |
| BMOV | Gho Pharma | Burns | II |
| BNP-001 | Scil Biomedicals | Psoriasis | II |
| Botox Cosmetic | Allergan | Wrinkling, skin | L-2001 |
| Chrysalin | Chrysalis Biotechnology | Ulcer, diabetic | II |
| CryoCeal | XCELLentis | Ulcer, venous | II |
| Daivobet | Leo | Psoriasis | L-2001 |
| Dapsone[1] | Atrix Laboratories/Fujisawa | Acne | III |
| | Atrix Laboratories | Dermatitis, atopic | IND |
| | Atrix Laboratories | Pruritus | I |
| Dehydroepiandrosterone Sulfate | Pharmadigm | Burns | II |
| Denileukin Diftitox[1] | Ligand | Psoriasis | II |
| DermiCol | Colbar | Wrinkling, skin | Clinical |
| Desloratadine[1,2] | Schering-Plough | Urticaria, idiopathic | L-2001 |
| Diltiazem[1] | Solvay/SLA Pharma | Fissure, anal | III |
| Dimericine | AGI Dermatics | Xeroderma pigmentosum | III |
| Doramapimod | Boehringer-Ingelheim | Psoriasis | II |
| Doxercalciferol | Bone Care International | Psoriasis | I |
| Dutasteride[1,2] | GlaxoSmithKline | Alopecia | II |
| Efalizumab[2] | Genentech/Xoma | Psoriasis | Prereg |
| E-Matrix | Encelle/Smith & Nephew | Ulcer, diabetic | I |
| EO-1606 | Leo | Dermatitis | I |
| Etanercept[1,2] | Immunex/Wyeth | Psoriasis | III |
| Fibrostat | Biovail/Procyon | Scars | II |
| Fluasterone | Hollis-Eden | Psoriasis | I |
| Fluorouracil[1] | Dermik | Keratosis, actinic | L-2001 |
| Fontolizumab | Protein Design Labs | Psoriasis | I/II |
| HuMax-CD4 | Genmab | Psoriasis | II |
| IC-747 | Biogen/Icos | Psoriasis | II |
| rhIL-18bp | Serono | Psoriasis | I |
| Ilodecakin | Schering-Plough | Psoriasis | II |
| Imiquimod[1,2] | 3M Pharmaceuticals | Keratosis, actinic | III |
| Infliximab[1] | Centocor | Psoriasis | III |
| ISAtx-247 | Isotechnika | Psoriasis | II |
| ISIS-104838 | Isis Pharmaceuticals | Psoriasis | II |
| KB-261 | Karo Bio | Atrophy, cutaneous | I |
| rhLactoferrin | Agennix | Ulcer, diabetic | I/II |
| Levocetirizine | UCB | Urticaria, idiopathic | L-2001 |

*Continuation*

# Annual Update 2003: Dermatologic Drugs

| Drug | Source | Condition | Phase |
|---|---|---|---|
| LyphoDerm | XCELLentis | Ulcer, venous | II |
| Maxacalcitol[1] | Chugai | Ichthyosis | L-2001 |
| | Chugai | Keratosis, palmoplantar | L-2001 |
| | Chugai | Psoriasis | L-2001 |
| MBI-594AN | Micrologix | Acne | II |
| MDI-101 | Molecular Design International | Acne | II |
| MDI-403 | Molecular Design International | Acne | II/III |
| Mepolizumab | GlaxoSmithKline | Dermatitis, atopic | II |
| MV-9411 | Miravant | Psoriasis | II |
| Nalfurafine Hydrochloride | Toray/Daiichi Pharmaceutical/Fujisawa | Pruritus | Prereg |
| NCX-1022 | NicOx | Dermatitis, atopic | II |
| NV-07a | Novogen | Photodamage | I |
| Olopatadine Hydrochloride[1,2] | Kyowa Hakko | Dermatitis | L-2001 |
| | Kyowa Hakko | Dermatitis, atopic | L-2001 |
| | Kyowa Hakko | Pruritus | L-2001 |
| | Kyowa Hakko | Psoriasis | L-2001 |
| | Kyowa Hakko | Urticaria | L-2001 |
| Onercept | Serono | Psoriasis | II |
| Orcel | Ortec | Burns | L-2002 |
| | Ortec | Epidermolysis bullosa | R-2001 |
| | Ortec | Ulcer, diabetic | II |
| | Ortec | Ulcer, venous | II |
| Paclitaxel[1,2] | Angiotech Pharmaceuticals | Psoriasis | II |
| PCL-016 | Novactyl | Acne | II |
| PH-10 | Provectus | Keratosis, actinic | I |
| | Provectus | Psoriasis | I |
| Pimecrolimus[2] | Novartis | Dermatitis, atopic | L-2002 |
| | Novartis | Eczema | L-2002 |
| | Novartis | Psoriasis | II |
| Pimilprost[2] | Sumitomo | Ulcer, skin | Prereg |
| Polyheal 1 | Polyheal | Ulcer, cutaneous chronic | R-2002 |
| PV-702 | GroPep | Ulcer, venous | II |
| PVAC | Corixa/Genesis Res. and Dev./Zenyaku Kogyo | Psoriasis | II |
| QRX-101 | QUATRx Pharmaceuticals | Psoriasis | II |
| Repifermin | Human Genome/GlaxoSmithKline | Ulcer, venous | II |
| Siplizumab[2] | MedImmune/Biotransplant | Psoriasis | II |
| Solarase | Quintiles/SkyePharma | Keratosis, actinic | L-2001 |
| SRP-299 | SR Pharma/Genesis Research and Development | Dermatitis, atopic | II |
| T-487 | Tularik | Psoriasis | I |
| Tacrolimus[1] | Fujisawa | Psoriasis | II |
| TAK-427 | Takeda | Dermatitis, atopic | II |
| Tazarotene[1,2] | Allergan | Photodamage | R-2002 |
| Thymosin β4 | RegeneRx Biopharmaceuticals | Ulcer, cutaneous chronic | IND |
| Trafermin | Kaken | Ulcer, skin | L-2001 |
| TU-2100 | Tamarkin/Ist. Biochim. Ital. Giovanni Lorenzini | Acne | II/III |
| | Tamarkin | Dermatitis, seborrheic | II |
| | Tamarkin | Hair growth abnormality | II |
| | Tamarkin | Psoriasis | II |
| Velac | Connetics | Acne | III |
| Vibrilase | BioMarin | Burns | I |
| Vitrix | Organogenesis | Ulcer, diabetic | II |
| VX-148 | Vertex | Psoriasis | II |
| Zorcell | Immune Response | Psoriasis | II |

[1]Launched for another indication. [2]Monograph previously published in Drugs of the Future. [3]Launched in 2000 for actinic keratosis.

# Compendium of Dermatologic Drugs

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## Psoriasis

Psoriasis is an inherited chronic inflammatory cutaneous disorder characterized by papulosquamous lesions appearing most frequently on the scalp, knees, elbows and torso. The nails, palms, soles, genitals and, rarely, face may also be affected. Lesions are frequently symmetrical, appearing in the same location on both sides of the body. Psoriasis affects approximately 2% of the population in the U.S. and Europe, with a somewhat lower prevalence in Asia and Africa. Currently some 7 million Americans are affected, and approximately 150,000-260,000 new cases of psoriasis are reported each year in the U.S. According to estimates provided by the National Psoriasis Foundation, the annual outpatient costs for treating psoriasis are in the range of USD $1.6-$3.2 billion. Indirect costs are also significant: the National Psoriasis Foundation estimates that approximately 56 million work hours are lost each year as a result of the disease.

Therapy for psoriasis is based on disease severity, which is measured according to the percentage of body area involved. Conventional topical treatments for psoriasis include emollients, keratolytics (salicylic acid), DNA synthesis inhibitors (coal tar and anthralin), antiinflammatory corticosteroids, vitamin D analogues and photodynamic therapy (PDT). Systemic treatments include cytotoxic agents (methotrexate), immunosuppressants (ciclosporin) and retinoids (etretin and tazarotene).

### *Vitamin D analogues*

Topical vitamin $D_3$ analogues such as calcitriol ($1,25(OH)_2D_3$) inhibit keratinocyte proliferation and have provided the basis for the clinical use of vitamin $D_3$ receptor agonists in psoriasis. Vitamin D analogues have also shown moderate immunomodulatory effects, which may contribute to their antipsoriatic efficacy. The most widely used topical calcitriol analogue for psoriasis is calcipotriol (Dovonex®), which has been marketed for more than 10 years for this indication.

An ointment formulation of Chugai's vitamin D analogue **maxacalcitol** (Oxarol®) was launched as an antipsoriatic agent in Japan in 2001. This product was previously available as an injectable formulation for the treatment of secondary hyperparathyroidism in patients with chronic renal failure associated with maintenance dialysis. Licensee Schering-Plough has discontinued development of maxacalcitol for psoriasis in the U.K. and U.S.

Basilea Pharmaceutica's **BAL-2299** is an oral vitamin $D_3$ congener that shows significantly better separation between epidermal effects and unwanted hypercalcemia than calcitriol or other vitamin $D_3$ analogues in preclinical models. BAL-2299, currently in phase IIa clinical testing, is being developed as a novel first-line oral treatment for plaque-type psoriasis.

An oral formulation of **doxercalciferol** (Hectorol™), a vitamin D analogue marketed in the U.S. and Canada by Bone Care International as a treatment for secondary hyperparathyroidism, is in phase I for the new indication of psoriasis.

In January 2003, the FDA cleared QUATRx Pharmaceuticals' IND for its novel vitamin D analogue **QRX-101**, allowing the company to initiate a double-blind, placebo-controlled phase II study of different concentrations of a topical formulation of the compound in patients with mild to moderate psoriasis. The trial will enroll 120 patients across 9 sites in the U.S. and aims to determine efficacy trends with increasing concentrations of QRX-101, compare safety and tolerability with vehicle, and select one or two concentrations for further evaluation. QUATRx acquired the exclusive license to QRX-101 from Deltanoid in 2002.

### *Retinoids*

Retinoids such as Allergan's **tazarotene** (Tazorac®), Zorac® inhibit the expression of various genes that affect keratinocyte hyperproliferation, abnormal differentiation, inflammation and immune cell functions. Tazarotene, marketed since 1996 for the treatment of psoriasis (and

*Table I: T-cell activation inhibitors recently launched or in development for the treatment of psoriasis (from Prous Science Integrity).*

| Drug Name | Source | Mechanism of Action/Description | Status |
|---|---|---|---|
| Alefacept | Biogen | Dimeric fusion protein that consists of the extracellular CD2-binding portion of human LFA-3 linked to the Fc portion of human $IgG_1$ | L-2003 |
| Efalizumab | Xoma | Chimeric anti-CD11a MAb | Prereg. |
| Denileukin Diftitox | Ligand | Recombinant DNA-derived cytotoxic fusion protein designed to direct the cytocidal action of diphtheria toxin to cells expressing the high-affinity IL-2 receptor on their surface | Phase II |
| ZorcellTM | Immune Response | Combination of two peptides derived from T cell receptors (Vβ3, Vβ13.1) in incomplete Freund's adjuvant | Phase II |
| HuMax-CD4 | Genmab | Fully human $IgG_1$ anti-CD4 monoclonal antibody | Phase II |
| Siplizumab | MedImmune/Biotransplant | Humanized anti-CD2 monoclonal antibody | Phase II |

since 1997 for the treatment of acne), is a fairly selective retinoid A receptor (RAR) ligand and is applied topically. Other retinoid agents are formulated for oral administration.

Ligand Pharmaceuticals is evaluating capsule and gel formulations of the retinoid RXR agonist **bexarotene** in phase II studies for psoriasis. Bexarotene (Targretin®) has been marketed since 2000 for the treatment of cutaneous T cell lymphoma.

Allergan's retinoid RAR antagonist **AGN-194310** is in phase III testing for psoriasis.

*Inhibitors of T-cell activation*

T-cells are known to play a pivotal role in the pathogenesis of psoriasis, although the nature of the agent inducing T-cell activation is still a matter of debate.

Biogen's **alefacept** (Amevive®) is a systemic immunosuppressive therapy that works by helping to rebalance the overactive cells in the immune system that cause psoriasis. It induces dose-dependent reductions in $CD4^+$ and $CD8^+$ T-lymphocyte counts. The drug was launched in the U.S. at the end of January 2003 as the first biologic therapy for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or PDT. Development of the drug in Europe has seen some setbacks, with the EMEA requesting additional clinical information leading Biogen to withdraw its marketing application there.

**Denileukin diftitox** (Ontak®), DAB389IL-2) is a fusion protein combining the enzymatic and membrane-translocating domains of diphtheria toxin with IL-2. Activated T-cells express the high affinity receptor for IL-2 and can bind DAB389IL-2. In psoriasis lesions most T-cells present are activated and express the IL-2 receptor. By binding to the IL-2 receptor, DAB389IL-2 is internalized and induces cell death selectively. Ligand is conducting phase II trials of denileukin diftitox in the treatment of psoriasis. The product has been marketed for some years as a treatment for cutaneous T-cell lymphoma.

**Efalizumab** (RaptivaTM) is being developed for the treatment of moderate to severe plaque psoriasis. Efalizumab is a humanized monoclonal antibody and acts as a targeted T-cell modulator designed to inhibit three key inflammatory processes in the cascade of events that are associated with psoriasis.

Efalizumab is being developed in the U.S. through a partnership between Genentech and Xoma. Serono has acquired a license for marketing the product outside of the U.S. and certain other Asian countries.

Table I presents information on these and other T-cell activation inhibitors in active development for the treatment of psoriasis, including their status of development for this indication.

*Cytokine-targeted therapy*

Cytokines are a family of polypeptides secreted by a large variety of cells in response to contact with differing stimuli. They have autocrine, paracrine and/or endocrine effects and are fundamentally implicated in the mediation and regulation of immune and inflammatory reactions. Chemokines (chemotactic cytokines) are a superfamily of 8- to 10-kDa polypeptides that act as chemical messengers to recruit and activate leukocytes to injured or inflamed tissues. Different chemokines have been associated with the inflammatory process occurring in psoriasis.

Information on cytokine- and chemokine-targeted therapies for psoriasis and their status of development for this indication is given in Table II.

*Agents targeting adhesion molecules*

Cellular adhesion molecules (CAMs) are a class of cell surface proteins belonging to the Ig supergene family that are involved in the binding together of cells in tissues. Several drugs targeting CAMs are in early-stage development for psoriasis.

Intercellular adhesion molecule-1 (ICAM-1) is an inducible member of the immunoglobulin superfamily of CAMs that can be expressed on endothelial cells, antigen-presenting cells and other cell types. ICAM-1 plays a

*Table II: Cytokine- and chemokine-targeted therapies for psoriasis (from Prous Science Integrity®).*

| Drug Name | Source | Mechanism of Action/Description | Status |
|---|---|---|---|
| Etanercept | Immunex/Wyeth-Ayerst | TNF-α antagonist, TNF receptor (human) fusion protein | Phase III |
| Infliximab | Centocor | Chimeric anti-TNF-α monoclonal antibody | Phase III |
| ISIS-104838 | Isis Pharma. | Antisense oligonucleotide, TNF-α production inhibitor | Phase III |
| Adalimumab | Abbott | Anti-TNF-α monoclonal antibody | Phase II/III |
| Ilodecakin | Schering-Plough | Human IL-10 | Phase II |
| Onercept | Serono | Recombinant tumor necrosis factor binding protein type 1 | Phase II |
| Pimecrolimus | Novartis | Cytokine production inhibitor | Phase II |
| Fontolizumab | Protein Design Labs | SMART anti-IFN-γ antibody | Phase I/II |
| rhIL-18bp | Serono | Recombinant human IL-18 binding protein | Phase I |
| T-487 | Tularik | Chemokine CXCR3 antagonist | Phase I |

pivotal role in leukocyte adherence and migration and important accessory roles in the activation of immune and inflammatory cells. Evidence shows that by blocking or downregulating ICAM-1, it is possible to interfere with the activation of immune and inflammatory cells and the trafficking of those cells to sites of inflammation, thereby potentially suppressing disease expression in a wide variety of inflammatory conditions. ICAM-1 is greatly overexpressed in involved tissues and thereby implicated in the pathogenesis of all these disease states.

**Alicaforsen sodium** is a phosphorothioate oligodeoxynucleotide antisense drug designed to inhibit expression of ICAM-1. A topical formulation of alicaforsen is being developed by Isis Pharmaceuticals for the treatment of patients with mild to moderate plaque psoriasis. Preclinical data on the topical formulation shows suppression of upregulated ICAM-1 and significant uptake by the epidermal and dermal skin layers implicated in the pathogenesis of psoriasis. Isis has initiated phase II studies of alicaforsen for psoriasis. The company is seeking a partner to collaborate in the clinical and market development of alicaforsen.

LFA-1, a cell adhesion molecule selectively expressed on leukocytes, has been shown to play a major role in the activation and trafficking of T-lymphocytes in the tissue at sites of inflammation. In the last decade a large body of preclinical data has accumulated to establish the importance of LFA-1 as a biological target, particularly in chronic, T-cell-driven inflammatory conditions and diseases. **IC-747**, an orally administered LFA-1 antagonist, is currently being evaluated in a phase IIa clinical trial designed primarily to assess the tolerability of the drug in patients with moderate to severe psoriasis. Icos and Biogen are collaborating on the development of this product.

Anti-L-selectin (**BNP-001**) – originally discovered by Protein Design Labs and now being developed by licensee Scil Biomedicals – is a recombinant monoclonal antibody of the immunoglobulin $G_4$ subclass ($IgG_4$) directed against the lectin domain of the adhesion molecule L-selectin on human leukocytes. It is proposed that the blocking of L-selectin might result in an interruption of the immunopathological changes in eruptive plaque-type psoriasis. BNP-001 is in phase I clinical trials.

The primary focus of Revotar Biopharmaceuticals, a majority-owned affiliate of Texas Biotechnology, is the development of **bimosiamose**, a small-molecule selectin antagonist licensed exclusively from Texas Biotechnology. It blocks the initial slowing of leukocyte traffic, prevents leukocytes from migrating into the tissue and may alter cell activation and cell-cell signaling pathways. Phase II trials with bimosiamose are expected to begin in the first half of 2003 using topically delivered formulations to treat psoriasis.

### *Angiogenesis inhibitors*

Angiogenesis is a complex process by which new blood vessels are formed from preexisting capillaries. In normal physiology, this process is under stringent control and occurs during embryonic development, ovulation, endometrial regulation and wound repair. However, many pathological conditions such as ischemic heart disease, atherosclerosis, psoriasis, rheumatoid arthritis, solid tumor growth, diabetic retinopathy and age-related macular degeneration appear to be driven by persistent upregulation of the angiogenic process. In psoriasis, angiogenesis results in an increased blood flow to affected areas, providing cells in the upper layer of the skin the nutrients they need to proliferate. By inhibiting the growth of new blood vessels to psoriatic plaques, antiangiogenic drugs may work to slow down the abnormal cell production that causes psoriasis.

Angiotech Pharmaceuticals and the U.S. National Cancer Institute have initiated an open-label pilot phase II study designed to determine if treatment with **micellar paclitaxel** at 4-week intervals for a total of 6 intravenous infusions is potentially efficacious in patients with severe psoriasis. Paclitaxel has been shown to disrupt inflammation, inhibit angiogenesis, reduce the production of tissue-destroying enzymes and block the uncontrolled proliferation of skin cells. Based on these studies, the company believes that paclitaxel may be an effective agent for the treatment of psoriasis.

AEterna has completed phase I/II testing of the angiogenesis inhibitor **AE-941** (Neovastat®), a naturally occurring antiangiogenic compound extracted from cartilage, in psoriasis. Although the drug is primarily targeted for oncology indications, the company is evaluating its options for further clinical trials in the psoriasis indication.

*Kinase inhibitors*

The p38 MAP kinase inhibitor **doramapimod** (BIRB-796) is in phase II development at Boehringer Ingelheim as an antipsoriatic agent.

*IMPDH inhibitors*

Inosine-5'-monophosphate dehydrogenase (IMPDH) catalyzes the reaction of inosine monophosphate, water and $NAD^+$ producing NADH and xanthosine 5'-monophosphate (XMP), which is the immediate precursor to guanosine monophosphate (GMP). Inhibition of IMPDH may be effective in inhibiting viral replication and proliferation of certain cell types (*e.g.*, lymphocytes). Compounds that inhibit IMPDH, a key enzyme in the *de novo* biosynthesis of guanosine nucleotides, inhibit the proliferation of B-cells and T-cells. The advantage of this approach is its specificity: no alternate pathways are available in the synthesis of these lymphocytes. Thus, the inhibition of IMPDH appears to be a very interesting target for immunosuppressive drugs.

In December 2002, Vertex initiated a phase II clinical trial evaluating an oral formulation of the second-generation IMPDH inhibitor **VX-148** in subjects with moderate to severe psoriasis.

*Immunomodulators*

Corixa is conducting phase II clinical trials of **PVAC™** treatment for use as an immunotherapeutic product for psoriasis. PVAC™ treatment is based on a proprietary process and formulation derived from heat-killed *Mycobacterium vaccae* developed by Corixa in collaboration with New Zealand-based Genesis Research and Development Corporation Limited. In August 2000, Corixa entered into a multiyear development, commercialization and license agreement with Medicis for the commercialization of PVAC™ in the U.S. and Canada. In August 1999, the company entered into a multiyear license, research and development agreement with Zenyaku Kogyo providing the latter with exclusive rights to PVAC™ in Japan.

**ISAtx-247** is a next-generation calcineurin inhibitor in phase II clinical development at Isotechnika as immunosuppressive therapy in organ transplantation and in the treatment of autoimmune diseases. Early studies indicate that ISAtx-247 is considerably more potent and less toxic than other immunosuppressants in this drug class, such as ciclosporin. ISAtx-247, currently in North American phase II trials for the treatment of moderate to severe psoriasis, is being codeveloped with Roche.

Fujisawa's **tacrolimus**, an immunomodulating calcineurin inhibitor marketed since 1993 for the treatment of transplant rejection (as Prograf®) and since 1999 for atopic dermatitis (as Protopic®), is in phase II testing for the new indication of psoriasis.

Hollis-Eden presented results from a preclinical study of HE-2500 (**fluasterone**) at the Third International Congress on Autoimmunity in February 2002, indicating that high doses of the immunoregulatory hormone reduced disease severity in a mouse model of psoriasis. Hollis-Eden has access to HE-2500 through its relationship with Aeson Therapeutics. The compound is in phase I for psoriasis, multiple sclerosis, SLE and arthritis, and is also undergoing phase II clinical trials for metabolic syndrome.

*Photodynamic therapy*

Photodynamic therapy (PDT) consists in the controlled administration of ultraviolet light in combination with a photosensitizing agent. This procedure has been used for more than 70 years. Approximately two-thirds of psoriasis patients will improve with PDT, with remissions lasting anywhere from a few days to a few months (average 3-6 months).

The photosensitizing agent **PH-10**, administered topically and activated with green laser light, is being studied by Provectus in phase I clinical trials for the treatment of psoriasis. The drug's mechanism of action is believed to involve the creation, upon activation, of free radicals that eliminate diseased cells. Although in the early stages of clinical development, PH-10 has not elicited significant pain and the typical adverse side effects often seen with other similar compounds.

Miravant is conducting phase II trials of a topical gel formulation of **MV-9411**, a proprietary photoreactive drug, in the treatment of plaque psoriasis. MV-9411 and related compounds have the ability to achieve biological responses at substantially lower drug and light doses, thus reducing treatment times and the potential for side effects.

*Combination products*

Leo's **Daivobet®**, a combination product incorporating the vitamin D analogue calcipotriol and betamethasone dipropionate, was approved and launched for the first time in Denmark in 2001. It is indicated for the treatment of plaque psoriasis. Regulatory approval has since been obtained in Sweden, Norway, the U.K. and Canada.

*Miscellaneous agents*

Tamarkin's lead product **TU-2100** has been shown to be effective and safe in phase II clinical studies as a top-

ical medication for psoriasis. It is a dual-action prodrug, *i.e.*, conjugate of two biologically active molecules, particularly designed to penetrate the skin and exert a plurality of effects in the skin. No significant adverse effects have been observed in studies in animals and humans.

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**Atopic dermatitis**

Atopic dermatitis is a chronic, inflammatory, erythematous, pruritic, eruptive disorder of the skin that is highly variable in appearance. It is characterized by very dry skin associated with intense pruritus that triggers eczema, resulting in erythema and lichenification of the skin. Cutaneous hypersensitivity and hyperreactivity to environmental irritants and inhalant and food allergens are present in most atopic dermatitis patients. Atopic dermatitis is considered an allergic disease wherein genetic, environmental, immunologic and infectious factors all contribute to its etiology. Atopic dermatitis frequently develops in early infancy, with nearly 60% of all cases presenting in the first 12 months of life and 30% more before the age of 5 years. There are currently more than 15 million adults and children in the U.S. who suffer from atopic dermatitis.

Effective treatment of atopic dermatitis presents a challenge to both patients and physicians, and control, rather than cure, is the goal of treatment, although spontaneous remissions are known to occur in some cases. Pharmacological treatment includes oral antihistamines (preferably the older, sedating antihistamines) and tricyclic antidepressants, which are useful in controlling pruritus, while topical antiinflammatory agents (corticosteroids, hydroxyquinoline and tar) are the mainstay for treating inflammation. Immunomodulating therapy may be indicated in patients with widespread and difficult-to-treat cases. Other treatment options include PDT with ultraviolet B, psoralen plus high-intensity ultraviolet A (PUVA), narrow band UVA or the combination of UVA and UVB light.

*Corticosteroids*

Topical corticosteroids constitute the first line of treatment for atopic dermatitis and can be used in combination with antibiotics. In spite of their efficacy, however, their severe adverse effects (diabetes mellitus, osteoporosis, skin atrophy and growth suppression in children) prevent their prolonged use.

NicOx has developed **NCX-1022**, a topical product delivering a nitric oxide (NO)-releasing derivative of the steroid hydrocortisone, as a new treatment alternative for atopic dermatitis. NCX-1022 (NO-hydrocortisone) is in phase II for the treatment of atopic dermatitis.

*Retinoids*

Allergan's retinoid RAR antagonist **AGN-194310** is in phase III testing for atopic dermatitis.

*Inhibitors of inflammatory processes*

A wide variety of compounds directed toward the multiple immune and inflammatory pathways involved in atopic dermatitis are under development at this time. Important targets include IL-4 and IL-5, phosphodiesterases, chemokines and adhesion molecules.

**Olopatadine hydrochloride** (Allelock®), a mediator release inhibitor and histamine $H_1$ receptor antagonist, was introduced by Kyowa Hakko in Japan in 2001 for various dermatology indications including atopic dermatitis, cutaneous pruritus, urticaria and vulgar psoriasis.

**TAK-427**, a histamine $H_1$ receptor antagonist from Takeda, is in phase II studies in both Europe and Japan for the treatment of atopic dermatitis.

**Mepolizumab**, a monoclonal antibody directed to IL-5, is in phase II development at GlaxoSmithKline for the treatment of atopic dermatitis.

As mentioned earlier, **bimosiamose** is in development by Revotar Biopharmaceuticals under an exclusive license from Texas Biotechnology. Phase II trials of topical formulations of the drug are expected to begin in the first half of 2003 for the treatent of atopic dermatitis.

*Immunosuppressants*

**Pimecrolimus** (formerly SDZ-ASM-981), an ascomycin macrolactam derivative and selective inhibitor of inflammatory cytokines, has been successfully developed as a novel nonsteroidal topical treatment for atopic dermatitis. Clinical trials involving more than 1,700 adult and pediatric patients with atopic dermatitis have confirmed that pimecrolimus, which acts by inhibiting the production and release of inflammatory cytokines (IL-2 and TNF-$\alpha$) from T-cells, is able to reduce the itching and redness associated with eczema within 8 days of beginning treatment. The good tolerability of topical pimecrolimus has been demonstrated in infants as young as 3 months, and efficacy has been demonstrated in a wide range of patients. In December 2001, the U.S. FDA approved pimecrolimus (Elidel®) cream 1%) for the treatment of mild to moderate atopic dermatitis in patients aged 2 years and older. The drug, which is approved for short-term and intermittent long-term use in patients who do not respond to or are intolerant of conventional therapies, was launched for the first time in the U.S. in early 2002. It was subsequently approved and launched in Denmark for use in patients aged 3 months and older, and registration dossiers are being reviewed in several European countries under the Mutual Recognition Procedure. An oral formulation of pimecrolimus is in phase II testing for atopic dermatitis.

*Immunomodulators*

Some investigators have hypothesized that the increased prevalence of atopic disease over recent decades may be the result of a decrease over the same time period in the incidence of infectious diseases, especially tuberculosis and other mycobacterial infections. Based on this hypothesis, SR Pharma and collaborators at Genesis Research and Development have studied the therapeutic efficacy of administering mycobacterial antigens in the form of a killed *Mycobacterium vaccae*. The *M. vaccae*-based immunotherapeutic product **SRP-299** has been specifically developed as a novel treatment for allergic disorders. Treatment has been shown to induce regulatory T-cells that control the inflammatory response and hence suppress inappropriate Th2 activity, independently of Th1 activity. Extensive evidence from preclinical allergy models conducted in 5 separate research centers has demonstrated beneficial immunological changes following SRP-299 treatment, including reduced levels of IL-5, induction of IL-10, suppression of IgE antibody and amelioration of airway hypersensitivity. These results are indicative of regulatory T-cell effect and downregulation of Th2 response. SRP-299 is currently in phase II testing in the U.K. and Ireland in children with moderate to severe atopic dermatitis.

Another *M. vaccae*-based vaccine is Genesis Research and Development's **AVAC**™. In November 2001, Genesis and SR Pharma announced an agreement for the joint development of a treatment for atopic dermatitis. Under the new agreement, the companies will merge each of their existing *M. vaccae*-based atopic dermatitis programs and select the most effective therapeutic. When trials evaluating both *M. vaccae*-based products are completed, the companies will select the most effective candidate for further clinical development and licensing. Genesis and SR Pharma will share commercial returns from whichever product is licensed. The companies reported in March 2003 the successful completion of a phase I pediatric trial of AVAC™. The study was conducted in New Zealand in 12 children aged 5-16 years. All children received 3 intradermal injections of AVAC™ at intervals of 2 weeks. AVAC™ demonstrated a good safety profile and was well tolerated. A placebo-controlled phase II trial in children with eczema is scheduled to begin in the second quarter of 2003. A phase I trial in adults was also completed in 2002.

*Antimicrobial agents*

Atrix Laboratories has filed an IND to begin clinical evaluation of Atrisone™ for the treatment of atopic dermatitis. The active compound in Atrisone™ is **dapsone**, an antibiotic with independent antiinflammatory activity. Dapsone is highly lipophilic and previously has only been commercially available as an oral tablet. The Atrix SMP technology provides a platform for highly water-insoluble drugs, such as dapsone, to be delivered topically, right at the site of disease.

*Serine protease inhibitors*

$\alpha_1$-Antitrypsin (AAT) is a glycoprotein primarily produced by hepatocytes, and to a lesser extent, immune system cells. AAT belongs to a family of structurally related proteins classified as serine protease inhibitors or SERPINS, which are known to inhibit several proteases including trypsin, cathepsin G, thrombin, tissue kallikrein, as well as neutrophil elastase. The proteinase/antiproteinase balance is believed to be important for maintaining healthy skin. Alterations in local tissue proteinase/antiproteinase balance, resulting from genetic or environmental factors, may lead to an increased susceptibility to inflammatory diseases of the skin such as atopic dermatitis and psoriasis.

In November 2002, ProMetic Life Sciences and Arriva Pharmaceuticals announced that their joint venture, Arriva-ProMetic Inc., had received approval from the U.S. FDA and Health Canada to initiate a clinical trial evaluating **recombinant $\alpha_1$-antitrypsin (rAAT) topical gel** (Dermolastin™) in patients with atopic dermatitis. The rAAT contained in this proprietary gel formulation is produced from yeast, which unlike commercially available forms of plasma-derived AAT, eliminates the risk associated with blood-borne infectious agents. Production of rAAT in yeast cells allows for the manufacture of large quantities of the protein therapeutic, an essential component of a clinical study program, thus enabling Arriva-ProMetic to commence clinical studies.

*Miscellaneous agents*

Arachnova has completed a phase IIa proof-of-concept study of its topical antidermatitis product **AA-10006** (Araderm™), a novel topical preparation of a known oral anxiolytic agent. When applied twice daily to affected areas, Araderm™ was found to improve symptoms of atopic dermatitis, with a 49% reduction in the primary efficacy variable –the mean SCORAD (SCORing Atopic Dermatitis) total score after one month of treatment– compared with a 31% reduction on placebo. Statistically significant differences between test compound and placebo were also seen in several other important variables, including the percent reduction in SCORAD total score at day 15, withdrawals due to lack of efficacy, percent reduction in spread of dermatitis and number of patients achieving a SCORAD objective score of < 9, considered clinically cured (37% *vs.* 14%). Araderm™ has been established as a stable, nonirritating and nonsensitizing compound for atopic dermatitis and associated conditions, and is protected by an international patent estate.

Leo has reported a compound in development for atopic dermatitis – **EO-1606** – for which the mechanism

of action has not yet been described. EO-1606 is in phase I clinical testing.

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### Miscellaneous eczema

*Retinoids*

**Alitretinoin**, a retinoid RXR and RAR agonist, is in phase II at Basilea Pharmaceutica as an oral agent for treating chronic hand eczema. Alitretinoin is a derivative of retinoic acid, a therapeutic class of compounds with proven efficacy in dermatology, including acne, psoriasis and other keratinizing dermatoses, as well as oncology. Alitretinoin has demonstrated activity in chronic hand eczema refractory to conventional therapy in an open-label clinical trial. The drug is already marketed (as Ligand's Panretin™) for the treatment of cutaneous lesions in patients with Kaposi's sarcoma.

Ligand Pharmaceuticals is evaluating a gel formulation of **bexarotene** in phase II studies for the treatment of chronic severe hand dermatitis.

Allergan's retinoid RAR antagonist **AGN-194310** is in phase III testing for atopic eczema.

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### Acne

Acne is a disorder resulting from the action of hormones on the sebaceous glands, which leads to plugged pores (blackheads and whiteheads), pimples, and even deeper lumps (cysts or nodules) that occur on the face, neck, chest, back, shoulders and even the upper arms. Acne affects nearly 85% of people between the ages of 12 and 24 years to some extent. However, the disease is not restricted to any age group; adults in their 20s and even into their 40s can and do get acne. While not a life-threatening condition, acne can be upsetting and disfiguring, and when severe, can lead to serious and permanent scarring. Nearly 17 million people in the U.S. have acne, making it the most common skin disease.

The goals of treatment are to heal existing lesions, stop new lesions from forming, prevent scarring and minimize the psychological stress and embarrassment caused by this disease. Drug treatment is aimed at reducing several problems that play a part in causing acne: abnormal clumping of cells in the follicles, increased oil production, bacteria and inflammation.

Analysts estimate that the U.S. market for treating mild to moderate acne is USD $0.7 billion, while worldwide this market may be in the range of USD $2-3 billion.

*Antimicrobial agents*

As mentioned above, Atrix Laboratories has filed an IND for Atrisone™ (**dapsone**) for the treatment of atopic dermatitis. The compound is also being codeveloped by Atrix and Fujisawa for the treatment of acne and is in phase III clinical evaluation for this indication.

Connetics has begun a phase III program for **Velac™** gel, a first-in-class combination of tretinoin (0.025%) and clindamycin phosphate (1%) for the treatment of acne. Two phase III trials will run concurrently and enroll 2,000 patients in total. Connetics has signed a development and commercialization agreement with Yamanouchi granting Connetics rights to develop and commercialize Velac™ gel exclusively in the U.S. and Canada, and nonexclusively in Mexico. Clinical development is ahead of schedule, and a revised launch date of mid-2005 has been issued.

**MBI-594AN** is a novel topical antibiotic for the treatment of acne. MBI-594AN is currently in phase IIb clinical development at Micrologix. Results from the company's preclinical research program demonstrated that MBI-594AN is nontoxic and nonirritating in animal models. In addition, MBI-594AN demonstrates excellent activity against resistant *Propionibacterium acnes* strains, suggesting that this agent may be more effective than currently available antibiotics. In January 2003, Micrologix began enrolling patients in a phase IIb study of MBI-594AN. The randomized, double-blind, placebo-controlled, dose-ranging efficacy study is treating 240 acne patients with placebo or MBI-594AN 1.25% or 2.5% twice daily for 12 weeks. The activity of MBI-594AN will be assessed based on reduction in acne lesion counts and physician's global assessment.

Bioresearch Italia announced in late 2002 that enrollment of healthy volunteers in a U.K.-based phase I trial of **BI-K0376** has been completed. The double-blind, placebo-controlled, dose-ranging study is assessing the safety and tolerability of BI-K0376 topical formulations after 4 weeks of twice-daily application to the face. Data will also be collected on the microbiological activity of the antibiotic on skin flora. Results are expected by the end of the first quarter of 2003. BI-K0376 is selective against *P. acnes*, including bacteria resistant to other antibiotic treatments, but spares normal skin bacterial flora.

Patient enrollment has begun in Novactyl's first phase IIa trial of **PCL-016** for the treatment of mild to moderate acne. In the study, to be conducted at Washington University School of Medicine, patients will receive topical treatment with PCL-016 twice daily for 12 weeks. The study will provide further information on the safety profile of the drug and initial information on efficacy in this patient population. PCL-016 targets the zinc finger proteins (ZFP) involved in a wide range of infective disorders. In preclinical trials, PCL-016 proved active against *P. acnes*.

*Retinoids*

Molecular Design International's **MDI-403** is a novel patented 13-*cis* retinoic acid derivative that is safe and effective for the topical treatment of acne and for the

repair of photodamage. Safety has been clearly demonstrated in preclinical toxicology and phase I clinical trials. Pilot phase II clinical trials again demonstrated safety. The drug is not irritating to human skin and is not teratogenic, which gives MDI-403 a marketing advantage over other retinoids. MDI-403 is currently in phase II/III clinical trials, and is available for licensing.

**MDI-101** is an all-*trans* retinoic acid derivative, also from Molecular Design International, that is being developed as a new topical antiacne agent. Preclinical studies have shown lower teratogenicity and better local tolerance than all-*trans* retinoic acid preparations. Currently in phase II clinical trials, the company is seeking a partner to license this product for further development. MDI-101 is also expected to have excellent potential for treating photoaging.

In addition to its other indications, Allergan's **AGN-194310** is in phase II testing for nodular acne.

*Photodynamic therapy*

Dusa's Levulan® (**aminolevulinic acid**), a targeted technology for the PDT of various skin conditions, is in phase I/II testing for the treatment of acne. A study has been completed using a nonlaser red light source illuminator with the product, designed to determine the effective dose for this indication. A new study is scheduled to begin shortly and will employ Dusa's nonlaser blue light source as well as the proprietary Kerastick™ applicator to determine the efficacy of these products in treating acne.

*Steroid 5α-reductase inhibitors*

Serono is evaluating the steroid 5α-reductase type 1 inhibitor **AS-601811**, a potential treatment for acne, in phase I clinical trials.

*Oral contraceptives*

In February 2002, Health Canada approved Wyeth's **Alesse™**, an oral contraceptive containing ethinylestradiol and levonorgestrel, for the treatment of moderate acne in women. Clinical trials in Canada and other countries enrolled 721 women with acne. Of those receiving Alesse™, 56.9% reported clear or almost clear complexion after 6 months of treatment, and 88% self-assessed their acne as improved after 6 menstrual cycles of therapy. Alesse™ is also under FDA review for this expanded indication.

*Miscellaneous agents*

As mentioned above, Tamarkin's lead product **TU-2100** is a dual-acting prodrug that is in development for psoriasis. This compound has also been shown to be effective as a topical medication for acne and codevelopment partner Istituto Biochimico Italiano Giovanni Lorenzini has initiated European phase II/III trials evaluating TU-2100 in this condidition.

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**Actinic keratosis**

Actinic keratosis (also known as solar keratosis) is a premalignant superficial skin condition that is linked to ultraviolet light exposure. Ultraviolet radiation causes cellular DNA mutations and induces a state of relative immunosuppression that prevents tumor rejection. It can develop at any point during a lifetime, but most often appears between the ages of 40 and 80. Actinic keratosis lesions can range in size from 1-2 mm papules to large plaques, and occur primarily on areas of the body that receive the greatest sun exposure. Commonly affected sites are the balding scalp, forehead, face, ears, neck and back of the forearms and hands.

It is estimated that 60% of predisposed individuals older than 40 years have at least one actinic keratosis or solar keratosis. Usually, these people are fair-skinned, burn easily and tan poorly, as well as have occupations or hobbies that result in excessive sun exposure. Actinic keratoses are the most common premalignant lesions in humans in the U.S. If left untreated, approximately 10% of cases of actinic keratosis develop into squamous cell carcinoma.

Options for the treatment of actinic keratosis include surgical or chemical destruction of the lesions, topical drug therapy and PDT. The goals of treatment are to destroy the abnormal cells, preserve normal appearance and function, and avoid complications. Additional goals include maximizing the cost-effectiveness to the healthcare system and both convenience and cosmetic outcomes for the patient. Current treatments are associated with a high rate of clearance of lesions, but treatment can be painful, may create scarring and destroys some healthy tissue.

*Immune response modifiers*

Because patients often have multiple actinic keratoses and these lesions tend to recur, a safe and effective patient-applied therapy would be an advantage. A topical, patient-applied immune response modifier would induce cytokines locally at the lesion site and selectively destroy abnormal cells with little or no pain, cosmetically unacceptable side effects or destruction of healthy tissue. An immune response modifier would provide a high rate of clearance without the limitations of existing therapies, and might also provide protection against new lesions because it would enhance cell-mediated immune recognition of new lesions. In addition, treatment of areas adjacent to the visible lesions might also have an effect on subclinical lesions in areas of sun-damaged skin.

3M Pharmaceuticals is developing the immune response modifier **imiquimod** (Aldara™) for the treat-

ment of actinic keratosis. Phase III studies are under way in North America. If these phase III trials proceed on track, 3M expects to file the initial licensing dossier for this new indication in the third quarter of 2003. The first launch for this new indication could be as early as 2004 (third quarter) in the U.S.

*Antimetabolites*

Dermik's Carac™ is the first FDA-approved, once-daily topical formulation of the antimetabolite **fluorouracil**. Carac™ was approved in 2000 and launched in the U.S. in 2001 for the treatment of actinic keratosis. There is evidence that the metabolism of fluorouracil in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid. In this manner, fluorouracil interferes with the synthesis of deoxyribonucleic acid (DNA) and to a lesser extent inhibits the formation of ribonucleic acid (RNA). Since DNA and RNA are essential for cell division and growth, the effect of fluorouracil may be to create a thymine deficiency that provokes unbalanced growth and death of the cell.

*Photodynamic therapy*

In June 2001, Swedish authorities granted approval for PhotoCure's **aminolevulinic acid methyl ester** (Metvix®) for the treatment of actinic keratosis and basal cell carcinoma in patients in whom traditional therapies are considered less suitable. The treatment is particularly useful for lesions in cosmetically sensitive areas such as the face and scalp. Metvix® PDT involves the local application of a cream that is absorbed into the cancer cells, followed by activation of the drug through illumination with a proprietary red light source (Curelight). Metvix® PDT selectively kills the cancer cells and leaves the normal skin intact. PhotoCure began selling Metvix® in Sweden in October 2001.

**PH-10**, in development for the treatment of psoriasis (see above), is also being studied by Provectus in phase I clinical trials to treat actinic keratosis.

*Nonsteroidal antiinflammatory drugs*

Another product for the actinic keratosis indication was launched for the first time in 2001 in Germany and the U.K. **Solaraze™**, a topical gel containing diclofenac sodium, was developed by SkyePharma and is marketed in collaboration with Quintiles. Solaraze™ utilizes SkyePharma's Hyaluronan Induced Targeting (HIT) transdermal delivery technology. Hyaluronic acid is a long-chained polysaccharide that is a major constituent surrounding cells in most animal tissues. Hyaluronic acid is attracted to and adheres to specific receptors on cell membranes which can be found in increasing numbers at sites of damage and disease in the body with a significant amount on the skin. This means that drugs can potentially be targeted to and held at the site where the drug is needed. Hyaluronic acid's safety profile, its ability to carry drug and its potential targeting characteristics make it an excellent vehicle for topical drug delivery.

*Enzyme replacement therapy*

AGI Dermatics' **Dimericine™** is applied topically to the skin once daily. The product uses a liposomal delivery vehicle (T4N5 liposome lotion) to deliver the bacteraial DNA repair enzyme T4 endonuclease V into the skin in order to reverse DNA damage caused by sunlight. A phase III trial has been conducted in patients with the genetic disease xeroderma pigmentosum who, due to a lack of DNA repair enzymes, easily develop skin cancer. Data indicated that the drug reduced the rate of skin cancer in xeroderma pigmentosum patients by 30% and reduced the precancerous form by 68%. Dimericine™ is being developed as a treatment for actinic keratosis.

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## Wounds

Wounds are a physical injury that results in an opening or break of the skin, and include cuts, scrapes, punctures, bites, burns, bruises and skin ulcers, to name a few. Each year, more than 4 million people suffer from chronic, nonhealing wounds such as diabetic ulcers, bedsores and venous ulcers. Diabetic foot ulcers alone affect more than 600,000 Americans each year. Inflammation and bacterial infection are two of the major problems that often contribute to delayed healing.

*Regenerative therapy*

Ortec's **OrCel™** (composite cultured skin) is a regenerative therapy consisting of bioengineered bovine collagen matrix seeded with epidermal and dermal cells. The product was approved by the U.S. FDA in 2001 for the treatment of fresh, clean split thickness donor site wounds in burn patients, and for the treatment of epidermolysis bullosa, a genetic disorder characterized by blisters and erosions in the skin. Ongoing phase II trials are evaluating the product in the treatment of diabetic foot ulcers and venous leg ulcers.

**CryoCeal**, a cryopreserved allogenic epithelial tissue product developed by XCELLentis (a subsidiary of Innogenetics), is in phase II testing. The product is targeted to the treatment of ulcers of the extremities, such as chronic leg ulcers. The ongoing phase II study is evaluating CryoCeal in patients with open leg ulcers of a mean duration of 21 months and an average ulcer size of 11 $cm^2$. Interim results reported after 24 weeks showed full wound closure in 11 of 27 patients. Final results of the study are expected in the first quarter of 2003.

The promising results obtained with CryoCeal pave the way for XCELLentis's next-generation wound care product, **LyphoDerm**. LyphoDerm consists of freeze-dried keratinocytes, the key factors that can stimulate and speed up the wound-healing process. A phase II randomized, open-label, parallel-group trial was initiated in Europe in September 2002. The study will evaluate the safety and efficacy of LyphoDerm during 10 weeks of product application plus 14 weeks of follow-up in 180 patients with hard-to-heal leg ulers.

**Vitrix™** is a living dermal replacement product developed by Organogenesis which is in phase II trials. This product is designed to replace dermal tissue that is lost in deep wounds, such as diabetic foot ulcers that extend down to bone, ligament or tendon. The loss of dermal tissue can seriously compromise wound healing, as the lack of dermal foundation impairs the normal healing process.

**E-Matrix™**, an injectable biopolymaterial developed by Encelle, has been shown to regenerate normal tissue in serious skin wounds. E-Matrix™ is a copolymer of a high-molecular weight protein and a high-molecular weight carbohydrate designed to mimic early fetal mesenchymal connective tissue. The product is unique in its ability to promote this rapid, nearly scarless healing process normally found only in early fetal development. As a result, E-Matrix™ treatment rapidly heals chronic ulcers recalcitrant to other conventional and experimental treatments. Encelle has completed a phase I study of the product and plans to conduct further studies in collaboration with development partner Smith & Nephew.

In November 2002, the Israeli company Polyheal Ltd. announced that it had been granted a CE Mark for its first proprietary product, the **Polyheal 1** medical device, for the treatment of various wounds. The product is a water-based suspension of nonbiodegradable, chemically inert, synthetic, charged microspheres, characterized by a narrow size distribution and an electrical charge. Polyheal 1 promotes the complex process of wound healing and tissue regeneration, induced by forming multipoint contacts with the cellular membrane. In clinical trials, Polyheal 1 was shown to accelerate granulation and reduce the healing time of numerous wounds including chronic ulcers, compared with longer healing times of other current treatments.

**Allox** is an allogeneic product consisting of skin cells secreting endogenous growth factors. It is currently being evaluated by IsoTis in a phase II clinical trial for the treatment of chronic skin wounds.

*Growth factors*

In April 2001, Kaken received Japanese marketing approval for **trafermin** (recombinant human basic fibroblast growth factor, Fiblast(R) spray) for the treatment of skin ulcers. Trafermin was launched there in June 2001.

**Repifermin** (recombinant human keratinocyte growth factor 2), a human protein that stimulates the repair of injured skin and mucosal tissue, is being developed by Human Genome Sciences in collaboration with GlaxoSmithKline. An ongoing phase IIb trial of topical repifermin has randomized 350 patients with chronic venous ulcers. Treatment and follow-up will be completed this year, and results will be reported before the end of 2003.

GroPep is currently evaluating **PV-702** as a topical treatment for chronic venous leg ulcers in a placebo-controlled phase II trial at 8 Australian study centers. Preclinical data generated by GroPep and its research partners in the Cooperative Research Centre for Tissue Growth and Repair have shown that the mixture of growth factors in PV-702 promotes key aspects of cellular behavior involved in the wound repair process, including cell division, cell migration and the synthesis of skin proteins such as collagen. PV-702 has also been shown to stimulate the healing of both normal and compromised wound repair in preclinical studies.

*Prostaglandins*

Sumitomo has filed with the Japanese health authorities for marketing approval of the stable prostaglandin $I_1$ analogue **pimilprost** (Skipron®) in the treatment of peripheral circulatory insufficiency, such as that occurring in skin ulcers.

*Therapeutic peptides*

RegeneRx Biopharmaceuticals has filed an IND to begin clinical testing of **thymosin β4** (TB4), a naturally occurring peptide and the major actin-sequestering molecule in mammalian cells. TB4 is found in significant concentrations in human wound and blister fluids and induces the production of laminin 5, which is responsible for the adhesion of certain cellular components of the skin. TB4 is found in highest concentrations in blood platelets. It can also influence T-cell differentiation, decrease toxicity induced by endotoxin and chemotherapy, and downregulate various key inflammatory cytokines and chemokines. The therapy may be administered topically and has been shown to significantly accelerate wound healing in normal, diabetic, steroid-suppressed and aged animal models.

The synthetic thrombin peptide **Chrysalin®** (TP-508) is being evaluated by Chrysalis Biotechnology in phase II trials for wound healing indications. Initial clinical trials are targeted to the treatment of diabetic foot ulcers, although the company plans to also study the product in patients with venous ulcers, infected wounds, burns and pressure sores. Preclinical studies have shown that a single application of the peptide can significantly accelerate the healing of open dermal wounds and surgical incisions. By stimulating the healing cascade through the thrombin receptor mechanism, a natural release of growth factors is activated.

*Debriding agents*

The treatment of burned skin in acute burn injuries requires the removal of this tissue to promote healing. This cleaning process is called debridement and can be performed using drug treatment or other nonsurgical methods, depending upon the location and depth of the wound. Currently marketed drug-based approaches to debridement have failed to gain wide acceptance in clinical practice, however, due to limited efficacy and slow onset of action, or pain and bleeding from digestion of healthy tissue.

BioMarin Pharmaceutical is developing **Vibrilase™**, a neutral zinc-containing protease secreted by the marine bacterium *Vibrio proteolyticus*, for this purpose. The company has initiated phase I trials evaluating topical Vibrilase™ in patients with serious burns.

*Miscellaneous agents*

Anoheal® is a 2% cream formulation of the calcium antagonist **diltiazem** (marketed for decades as an oral treatment for angina pectoris) developed by S.L.A. Pharma for the treatment of anal fissures. Applied topically, diltiazem relaxes the muscles around the anus, relieving pain and allowing fissures to heal without surgery. The amount of diltiazem in each application of Anoheal® is approximately one-tenth the dose given orally to treat angina. Solvay has acquired U.S. marketing rights to the product, which is currently in phase III testing.

Gho Pharma is developing the organic vanadium salt bis(maltolato)oxovanadium (**BMOV**) as a treatment for severe burns in children, a condition for which there are no currently available therapeutic drugs. BMOV limits or prevents the secondary injury that arises as a result of tissue damage caused by the actual burn trauma or primary injury. The company intends to seek orphan drug status for the treatment of severe burn wounds in children. No dose-related or dose-limiting side effects were observed at the anticipated therapeutic dose level in a phase I study evaluating BMOV in healthy volunteers. Gho Pharma plans to initiate a large, multicenter, pivotal study of BMOV in children with hot-water burns during 2003.

Pharmadigm's Inflarest™, an intravenous formulation of **dehydroepiandrosterone sulfate**, has completed phase IIa testing in hospitalized burn victims to evaluate its ability to accelerate wound closure. The androgenic steroid is a potent antiinflammatory agent that has been shown in preclinical models of severe thermal injury to accelerate wound closure and restore the skin barrier function.

Procyon and licensing partner Biovail have conducted a Canadian multicenter phase II trial of **Fibrostat®**, a topical cream for the treatment of excessive and hypertrophic scarring. Fibrostat® contains putrescine dihydrochloride as the active ingredient. This product is thought to inhibit and normalize the activity of the enzyme tissue transglutaminase (TTGase), which is implicated in the formation of excessive collagen cross-links resulting in excessive scarring. Based on the positive results obtained in this study, the partners plan to conduct further phase II trials.

**Recombinant human lactoferrin** (rhLF) has potential to speed the healing of chronic wounds and has been shown effective in preclinical models through enhancement of antimicrobial activity, induction of growth factor production and recruitment of various types of cells involved in wound repair. Topically applied rhLF promotes the extent and speed of wound healing relative to vehicle control. Lactoferrin has also demonstrated superior efficacy compared to a leading approved treatment for wound repair. Agennix plans to initiate a phase II clinical trial in the treatment of chronic wounds early in 2003.

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**Urticaria**

Urticaria (commonly called hives) is an itchy rash consisting of localized swellings of the skin that usually last for a few hours before fading away. Affecting an estimated 15-25% of Americans at least once in their lives, urticaria is a reaction to a variety of substances, including food, drugs and topical agents. Urticaria is usually the result of an allergic reaction that causes a release of histamine from cells in the skin. The histamine then causes the blood vessels to dilate and leak fluid, causing the skin to swell. This swelling irritates the nerve endings, which results in the itching sensation. An estimated 25% of urticaria patients develop chronic idiopathic urticaria, which is defined as a case that lasts for a period of at least 6 weeks and has no identifiable cause. Although it is uncomfortable, and cosmetically unacceptable, it is rarely dangerous. Severe urticaria, however, may sometimes cause swelling of the face and throat, resulting in difficulty breathing (anaphylaxis).

Antihistamines are the main treatment for urticaria to reduce the allergic response. In some instances, when first-line methods do not work effectively, a brief course of oral corticosteroids may need to be prescribed.

Two new-generation antihistamines were launched in 2001 for the indication of chronic idiopathic urticaria. In January 2001, UCB obtained the first approval from the German health authorities to market **levocetirizine** (Xyzal™/Xusal™), developed by UCB under license from Sepracor. Belonging to the class of nonsedating antihistamines, levocetirizine was approved for all three relevant indications in its class, *i.e.*, seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria. The product is characterized by a fast onset of action, outstanding efficacy and an excellent safety profile. The first launch took place in Germany in early February 2001. E.U.-wide approval of levocetirizine via the mutual recognition procedure was obtained in August 2001.

**Desloratadine** (Neoclarityn™) was developed by Sepracor as an improved version of the second-generation antihistamine loratadine that does not block cardiac potassium channels and thus possesses a superior cardiovascular safety profile. The product, which is manufactured and marketed by Schering-Plough, was approved in the E.U. in 2001 and in the U.S. in 2002 for the treatment of chronic idiopathic urticaria.

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## Pruritus

Pruritus is the medical term for itching. It may be associated with underlying systemic illnesses, viral infection or the healing of a burn or wound, and persistent pruritus should always be investigated by a physician. This differs from urticaria, which is associated with wheals, flares and reddening. Nonetheless, both conditions present with itching or pruritus.

### *κ-Opioid agonists*

Toray is developing an injectable formulation of **nalfurafine hydrochloride** (TRK-820), a novel, selective kappa-opioid receptor agonist for the treatment of uremic pruritus in patients receiving dialysis as a first indication. A marketing application for the product was filed in Sweden at the end of 2002. The drug is expected to be launched in Europe, where it will be marketed by Fujisawa, in 2004. Japanese development partner is Daiichi Pharmaceutical.

### *Antimicrobial agents*

Atrix Laboratories' Atrisone™ (**dapsone**) is being developed for the treatment of chronic itch associated with healed and healing burn wounds, and is currently in phase I trials for this indication.

## Cutaneous atrophy

Cutaneous atrophy is a condition where the skin becomes thin and loses some of its function. The negative consequences are easy bruising and impaired wound healing. Cutaneous atrophy typically results from topical treatment with glucocorticoids, but can also be caused by aging or sun exposure. In atrophied skin, there is a marked reduction of collagen, a protein that plays an important role in skin structure.

Karo Bio has demonstrated in animal models that thyroid hormone analogues such as **KB-261** can restore collagen production, measured as formation of procollagen, after exposure to strong steroids. Karo Bio has also obtained phase I clinical data indicating that KB-261 could be used for prevention of steroid-induced skin atrophy. The company is looking for a partner for further development of the product.

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## Photodamage

Changes in the skin due to prolonged exposure to sunlight can lead to structural damage resulting in wrinkling and photodamage. These changes can also cause pronounced suppression of the normal skin immune activity and at the same time damage to the DNA of skin cells. Together, these effects predispose to the development of skin cancers.

Novogen's **NV-07a** has been developed to repair the skin after damage caused by prolonged exposure to sunlight. While sun block creams have been the mainstay of skin protection from acute effects of sun exposure, they have not succeeded in reducing the incidence of certain types of skin cancer. Novogen has announced results from two phase I clinical trials in which immunosuppression and ongoing DNA damage were both ameliorated in the skin of human subjects who had been administered a topical skin cream containing NV-07a after sun exposure.

In addition to being marketed for psoriasis and acne for several years, Allergan's **tazarotene** was approved (Avage™) in October 2002 by the FDA for adjunctive use in the treatment of photodamage.

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## Wrinkling

Sun exposure, the environment, smoking and time are common causes of wrinkled or aged skin. Although the elimination or correction of wrinkles is an aesthetic rather than therapeutic issue, it is a common concern among patients visiting dermatology clinics.

In April 2001, Health Canada granted approval to Allergan's **Botox Cosmetic™** (botulinum toxin type A) for the temporary improvement in the appearance of moderate to severe glabellar lines in adult men and women 65 years of age or younger. The approval specifically applies to the vertical lines between the eyebrows. Botox Cosmetic™ is now marketed in both Canada and the U.S. for this use with dosing specific to treat frown lines.

ColBar's **DermiCol** is a uniquely formulated, injectable, cross-linked collagen filler designed for the long-term correction of soft tissue contour deficiencies such as facial wrinkles. The rationale for developing such a product emerges from the relatively short biodurability of existing products resulting in short term contour maintenance. DermiCol has been designed to have a slower resorption rate and longer biodurability than other collagen fillers, resulting in effective contour correction for a minimum of 2 years. DermiCol is in the process of obtaining CE Mark, and is currently undergoing premarketing clinical trials in Europe. DermiCol is slated to be launched for sale in

Europe by mid-2003. An IDE for DermiCol has been approved by the FDA.

### Ichthyosis

The ichthyoses are a family of genetic skin diseases characterized by dry, thickened, scaling skin. Dermatologists estimate that there are at least 20 varieties of ichthyosis, with a wide range of severity and associated symptoms. Ichthyosis, which affects more than 1 million Americans, can be a disfiguring disease, and as such has numerous social and psychological implications. There is no cure for ichthyosis, only treatments to help manage symptoms. Alpha-hydroxy acids (AHAs) are one effective treatment for the disease. Formulations containing up to 12% glycolic acid, lactic acid and its derivatives are typically used. Oral retinoids provide dramatic improvements in other patients.

Chugai's vitamin D analogue **maxacalcitol** (Oxarol®) ointment) was launched in Japan in 2001 for the treatment of psoriasis and several skin conditions, including ichthyosis.

### Palmoplantar keratosis

Palmoplantar keratoses are a group of mostly hereditary disorders characterized by thickening of the palms and soles. It occurs as a result of excessive keratin formation, which leads to hypertrophy of the stratum corneum (hyperkeratosis).

An ointment formulation of **maxacalcitol** (Oxarol®) was launched in Japan in 2001 for the treatment of palmoplantar keratosis, as well as other skin conditions.

### Hair growth abnormalities

Hair growth abnormalities include androgenic alopecia, inflammatory alopecia, alopecia areata, male pattern baldness, hirsutism and others. Analysts estimate that the U.S. market for hair growth disorders is approximately USD 1-2 billion, while the entire worldwide market is approximately USD 3 billion.

**Dutasteride**, a 5α-reductase inhibitor type 1 and type 2 inhibitor from GlaxoSmithKline, has been evaluated in phase II trials as a treatment for androgenic alopecia.

In addition to the other indications mentioned above, Tamarkin's **TU-2100** has also been shown to be effective and safe in phase II clinical studies for the treatment of hair growth disorders.

### Information Sources on the Internet

American Academy of Dermatology
www.aad.org
DermIS
www.dermis.net/index_e.htm

Foundation for Ichthyosis and Related Skin Types (FIRST)
www.scalyskin.org

National Institute of Arthritis and Musculoskeletal and Skin Diseases
www.nih.gov/niams

National Psoriasis Foundation
www.psoriasis.org

# Monograph Updates of Dermatologic Drugs

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## Adalimumab

Abbott recently began marketing adalimumab (D2E7, Humira™) for reducing the signs and symptoms and inhibiting the progression of structural damage in adults with moderately or severely active rheumatoid arthritis. Adalimumab is a fully human antibody that binds to human TNF-α, discovered through a collaboration between Abbott and Cambridge Antibody Technology. Approval for adalimumab in Europe is anticipated in mid-2003 and clinical trials are also in progress in juvenile rheumatoid arthritis and Crohn's disease (see *Drugs of the Future* 2003, 28(1): 83).

Abbott is now expanding its immunology clinical trials program to include trials of adalimumab in psoriasis and psoriatic arthritis. Clinical data have suggested th at treatments that inhibit TNF-α may be effective in these diseases. Abbott plans to begin a multicenter, randomized phase II trial in adult patients with moderate to severe chronic plaque psoriasis. Patients will be assessed by the Psoriasis Area and Severity Index (PASI) score. Meanwhile, a randomized, placebo-controlled phase III trial has already been initiated to evaluate the effect of adalimumab on signs and symptoms of psoriatic arthritis in adult patients with moderate to severe disease. Efficacy will be measured by improvements in ACR response (1).

1. *Abbott expands Humira development into psoriasis and psoriatic arthritis*. DailyDrugNews.com (Daily Essentials) March 5, 2003.

*Original monograph* - Drugs Fut 2001, 26(7): 639.

## AE-941

AEterna's AE-941, or Neovastat®, is an angiogenesis inhibitor extracted from marine cartilage that is currently in phase III evaluation for renal cell carcinoma, an indication for which the compound holds orphan drug status in the U.S. The company has completed two strategic partnership agreements with Ferrer and Medac for the marketing of Neovastat® in Europe and in Latin America. Neovastat® is also being evaluated in a phase III trial in lung cancer and a phase II trial in multiple myeloma in Canada, the U.S. and Europe (1-3). Other potential indications for the angiogenesis inhibitor include psoriasis and age-related macular degeneration (AMD). Based on the promising results from a phase I/II trial (see below), the company is currently reviewing alternatives to pursue continued development of Neovastat® in psoriasis.

AE-941 was administered orally to patients with psoriasis in a phase I/II trial in which 49 patients were randomized to receive a dose of 30, 60, 120 or 240 ml/day for 12 weeks. Although the 30 ml/day dose did not improve PASI scores, the other doses produced dose-related improvements of 30.8%, 41.7% and 50% for the 60, 120 and 240 ml/day doses, respectively. The treatment was safe and well tolerated at all doses (4).

1. *AEterna updates Neovastat progress*. DailyDrugNews.com (Daily Essentials) June 17, 2002.

2. *Orphan drug designation awarded to Neovastat in renal cell carcinoma*. DailyDrugNews.com (Daily Essentials) Nov 4, 2002.

3. Batist, G., Patenaude, F., Champagne, P., Croteau, D., Levinton, C., Hariton, C., Escudier, B., Dupont, E. *Neovastat (AE-941) in refractory*

*renal cell carcinoma patients: Report of a phase II trial with two dose levels*. Ann Oncol 2002, 13(8): 1259.

4. Sauder, D.N., Dekoven, J., Champagne, P., Croteau, D., Dupont, E. *Neovastat (AE-941), an inhibitor of angiogenesis: Randomized phase I/II clinical trial results in patients with plaque psoriasis*. J Am Acad Dermatol 2002, 47(4): 535.

*Original monograph* - Drugs Fut 2000, 25(6): 551.

## Alefacept

Biogen's alefacept (Amevive®) is a fully human fusion protein comprised of the first extracellular domain of LFA-3 fused to sequences of $IgG_1$. Alefacept is a systemic immunosuppressive therapy that works by helping to rebalance the overactive cells in the immune system that cause psoriasis. It induces dose-dependent reductions in $CD4^+$ and $CD8^+$ T-lymphocyte counts and the former should be monitored weekly during the 12-week dosing period and used to guide dosing. Alefacept is unique in that it has a long-lasting effect with the potential to provide patients with months free from both disease and treatment.

Alefacept was approved in January by the FDA as the first biologic therapy for the treatment of adults with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and launched several days later. However, the Committee for Proprietary Medicinal Products (CPMP), the advisory body of the European Medicines Evaluation Agency (EMEA), has requested additional information from Biogen relating to its application for alefacept for psoriasis. The company has withdrawn its application and plans to develop the additional clinical information requested to obtain approval in the E.U., which could take several years (1-6).

*In vitro* experiments with transfected Jurkat cells and IL-2-expanded NK cells (which express CD16) revealed that alefacept activates intracellular signaling pathways that ultimately induce the release of granzyme B, a serine protease involved in apoptosis. Alefacept appeared to act as an effector molecule that mediates the interaction of cells expressing CD2 and FcγR to activate FcγR-positive cells such as $CD16^+$ positive NK cells, which would then secrete granzyme and induce apoptosis of activated $CD2^+$ T-cells (7).

Comparison of gene expression revealed that the level of expression of several type 1 proinflammatory genes, such as IL-12p40, interferon gamma, the transcription factors STAT1 and IRF1, the chemokines IL-8 and MIG and iNOS (inducible nitric oxide synthase), increased in skin lesions of untreated psoriatic patients compared to nondiseased skin. Treatment with alefacept suppressed the expression of these genes, suggesting a mechanism of action independent of its effects on T-cell populations (8).

A randomized, placebo-controlled phase II trial evaluated the duration of clinical response following treatment with alefacept (0.025, 0.075 and 0.150 mg/kg i.v. weekly for 12 weeks) in 229 patients with psoriasis. Two weeks following treatment, 19 patients were clear or almost clear of the disease, with 84% maintaining this response for the duration of the 12-week follow-up period. During this latter period, 12 other patients continued to respond and improve. Of these patients, 26 enrolled in a second open-label study to evaluate response duration. No subsequent dose was required for a median of 10 months. The trials concluded that alefacept promotes lasting remission, with no disease rebound, and has a favorable safety profile in the treatment of psoriasis (9).

Two multicenter, randomized, double-blind phase III studies including more than 1,000 patients with chronic psoriasis reported clinically meaningful responses after administration of a 12-week alefacept course. The percentages of patients who achieved a > 50% reduction in the PASI score at the end of the treatment were 54-61% for treatment-naive patients and 52-56% for previously treated patients. Clinically meaningful responses after administration of alefacept were correlated with a better quality of life. A second 12-week alefacept course improved the PASI score, erythema, induration and desquamation compared to a single 12-week course of therapy (10-12). The results of these studies and some that follow are shown in Table I.

The safety profile for alefacept was shown to be good after a second 12-week treatment course. No cumulative effect on T-cells was detected, and no patient was hospitalized due to disease rebound after the end of treatment (13).

Data pooled from 3 placebo-controlled trials in 1,289 patients with plaque psoriasis showed that alefacept therapy was well tolerated after single and multiple courses. Headache (17%), accidental injury (15%) and infection (11%) were the most common adverse effects seen with alefacept 7.5 mg, alefacept 0.025, 0.075 and 0.15 mg/kg i.v. given each week and alefacept 10 or 15 mg given as weekly i.m. injections (14).

Placebo or alefacept (10 or 15 mg i.m.) was administered weekly to 507 patients with psoriasis in a 12-week, multicenter, randomized, double-blind phase III trial. Pharmacodynamic analysis showed that improvements in PASI scores were correlated with reductions in memory effector T-cells (15).

A multicenter, randomized, double-blind, placebo-controlled phase III clinical trial has shown that treatment with 2 courses of alefacept for 12 weeks each induces durable

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

| Indication | Design | Treatments | n | Conclusions | Ref. |
|---|---|---|---|---|---|
| Psoriasis | Open | Alefacept, 7.5 mg iv 1x/wk x 12 wk | 22 | Alefacept suppressed the expression of type 1 inflammation genes (*e.g.*, IL-12p40, IFNγ, IRF-1, STAT1, IL-8, MIG and iNOS) and reduced the number of disease-related memory $CD4^+$ and $CD8^+$ T-cells in psoriatic skin lesions | 8, 20, 22 |
| Psoriasis | Pooled/meta-analysis | Alefacept, 10 mg im 1x/wk x 12 wk<br>Alefacept, 15 mg im 1x/wk x 12 wk<br>Alefacept, 7.5 mg iv bolus 1x/wk x 12 wk (x 2 cycles)<br>Placebo x 12 wk → Alefacept, 7.5 mg iv bolus 1x/wk x 12 wk<br>Alefacept, 7.5 mg iv bolus 1x/wk x 12 wk → Placebo x 12 wk | 1000 | Alefacept administered im or iv for 12 weeks effectively reduced the severity of symptoms of chronic psoriasis. Additional symptom improvement was detected after a second 12-week iv course | 10 |
| Psoriasis | Pooled/meta-analysis | Alefacept, 10 mg im 1x/wk x 12 wk<br>Alefacept, 15 mg im 1x/wk x 12 wk<br>Alefacept, 7.5 mg iv bolus 1x/wk x 12 wk (x 2 cycles)<br>Placebo | 1060 | Alefacept administered im or iv was effective in patients with chronic plaque psoriasis. The drug was slightly more effective in treatment-naive patients than in previously treated patients | 11 |
| Psoriasis | Pooled/meta-analysis | Alefacept, 10 mg im 1x/wk x 12 wk<br>Alefacept, 15 mg im 1x/wk x 12 wk<br>Alefacept, 7.5 mg iv bolus 1x/wk x 12 wk (x 2 cycles) | | Clinical responses to alefacept in patients with chronic plaque psoriasis correlated with improvements in quality of life | 12 |
| Psoriasis | Double-blind, multicenter | Placebo x 12 wk → Alefacept, 10 mg 1x/wk x 12 wk<br>Alefacept, 10 mg 1x/wk x 12 wk → 10 mg 1x/wk x 12 wk<br>Alefacept, 15 mg 1x/wk x 12 wk → 15 mg 1x/wk x 12 wk | 375 | Administration of a second alefacept course was as safe as a first course and increased the benefits induced by the drug in patients with chronic plaque psoriasis | 13 |
| Psoriasis | Randomized, double-blind, multicenter | Alefacept, 7.5 mg iv bolus 1x/wk x 24 wk (n=183)<br>Alefacept, 7.5 mg iv bolus 1x/wk x 12 wk → Placebo x 12 wk (n=184)<br>Placebo x 12 wk → Alefacept, 7.5 mg iv bolus 1x/wk x 12 wk (n=186) | 553 | A single course of alefacept was well tolerated and significantly effective in improving PASI scores in patients with chronic plaque psoriasis. A second course of treatment increased the efficacy and was equally well tolerated | 16, 17 |
| Psoriatic arthritis | Open | Alefacept, 7.5 mg iv 1x/wk x 12 wk | 11 | The improvement in symptom scores and clinical joint counts found in patients with psoriatic arthritis who responded to alefacept administered for 12 weeks was associated with a reduction of T-cells in epidermis and synovial tissue | 21 |
| Psoriasis | Open | Alefacept, 7.5 mg iv 1x/wk x 12 wk | 9 | Alefacept reduced the epidermal thickness and the mean T-cell count (especially skin-homing, epithelial-homing and $CD8^+$ memory T-cells) in both the epidermis and dermis in patients with chronic plaque psoriasis | 23 |
| Psoriasis | Randomized Open | Alefacept, 15 mg im 1x/wk x 12 wk<br>Alefacept, 15 mg im 1x/wk x 12 wk + Narrow-band UV radiation x 6 wk<br>Alefacept, 15 mg im 1x/wk x 12 wk + Narrow-band UV radiation x 12 wk | | The combination of alecapt and narrow band UVB radiation showed a 75% improvement in symptom scores and had a good safety profile in patients with chronic plaque psoriasis | 24 |
| Scleroderma | Open | Alefacept, 7.5 mg iv 1x/wk x 12 wk | 8 | Alefacept induced a transient decrease in the levels of $CD3^+$, $CD4^+$ and CD8+ T-cells in both peripheral blood and bronchoalveolar lavage fluid in patients with scleroderma and lung inflammation, without affecting their FVC or diffusing capacity for CO | 25 |

clinical improvement in patients with chronic plaque psoriasis. A total of 553 patients received two 12-week treatment courses of either placebo or 7.5 mg of alefacept i.v. once weekly, separated by a treatment-free follow-up period of 12 weeks. After completion of the first 12-week course, alefacept was associated with a higher maximum mean reduction in the PASI score (47% *vs*. 20%) and a higher percentage of patients with > 75% PASI improvement (28% *vs*. 8%) compared to placebo. Administration of a second 12-week course of alefacept increased both the intensity of the drug's therapeutic effects and the duration of clinical response. Alefacept was well tolerated, and the incidence of adverse events tended to be lower during the second active treatment course. Quality of life was also significantly improved compared to placebo, an effect enhanced by repeated alefacept administration. Clinical responses to alefacept were correlated with reductions in memory effector T-cells ($CD45RO^+$) after both single and multiple treatment courses. The authors concluded that these results support the use of alefacept as an intermittent therapy for chronic plaque psoriasis (16-19).

Psoriatic patients who responded to alefacept showed significant reductions in the numbers of $CD3^+$, $CD8^+$ and $CD103^+$ T-cells in the epidermis and dermis of skin lesions, and also in those of specific memory or effector T-cells in peripheral blood, suggesting that alefacept specifically targeted psoriasis-inducing memory T-cells present in the lesions (20).

Patients with psoriasis and psoriatic arthritis who responded to treatment with alefacept also showed reductions in the number of T-cells in the epidermis and synovial fluid. The intensity of symptom improvement seemed to be especially associated with the level of reduction in $CD45RO^+$ T-cells (21).

The effects of alefacept on subpopulations of memory T-cells in 22 psoriatic patients were evaluated. Administration of a weekly dose of 7.5 mg of alefacept for 12 weeks selectively reduced the percentages of effector memory T-cells and type 1 (interferon gamma-producing) T-cells, but spared central memory T-cells and naive T-cells (22).

Administration of a weekly dose of 7.5 mg of alefacept for 12 weeks significantly reduced epidermal thickness in psoriatic patients. Response to treatment was associated with lower mean T-cell counts in both epidermis and dermis, especially the skin-homing, epithelial-homing and $CD8^+$ memory T-cells. This selective depletion of disease-related T-cells was suggested to induce antiinflammatory gene effects (23).

A randomized, open-label study evaluated the efficacy of combining alefacept (15 mg i.m. once weekly) and narrow-band ultraviolet light (NB UVB). Thirty psoriasis patients were randomized to receive alefacept alone for 12 weeks or alefacept combined with NB UVB 3 times a week until clear or for 6-12 weeks. The preliminary data showed that combination therapy induced a 75% reduction in the PASI score of all the patients who received it. Rash was the most common adverse event found with the combination therapy, and no opportunistic infections were reported in any patient included in the study (24).

The effects of alefacept on lung inflammation were assessed in 10 patients with scleroderma. Administration of 12 weekly i.v. infusions of 7.5 mg alefacept was well tolerated and decreased the levels of $CD3^+$, $CD4^+$ and $CD8^+$ T-cells in both peripheral blood and bronchoalveolar lavage fluid at 2 weeks after the end of therapy. T-cell recovery was suggested by the finding of higher cell levels at 3 months after the end of therapy. No changes in the forced vital capacity or the carbon monoxide-diffusing capacity of the patients were found throughout the study (25).

1. *Approval recommended for Amevive in psoriasis*. DailyDrugNews.com (Daily Essentials) May 24, 2002.

2. *Complete response letter issued for Amevive in psoriasis*. DailyDrugNews.com (Daily Essentials) June 14, 2002.

3. *Amevive application to be reviewed within six months*. DailyDrugNews.com (Daily Essentials) Sept 19, 2002.

4. *Biogen updates advances in late-stage pipeline*. DailyDrugNews.com (Daily Essentials) July 23, 2002.

5. *Delay announced in European approval for Amevive*. DailyDrugNews.com (Daily Essentials) Feb 21, 2003.

6. *First biologic therapy for psoriasis approved by FDA*. DailyDrugNews.com (Daily Essentials) Feb 4, 2003.

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15. Ortonne, J.P., Prinz, J., Barker, J., Dubertret, L. *Relationship between pharmacodynamic and clinical effects of alefacept in psoriasis*. Ann Dermatol Venereol 2002, 129(1, Book 2): Abst P2011.

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*Original monograph* - Drugs Fut 2001, 26(6): 527.

## Efalizumab

Efalizumab (hu1124, Raptiva™, formerly Xanelim™) is a recombinant, humanized anti-CD11a monoclonal antibody that is designed to target three key processes in events that lead to psoriasis – binding of T-cells through interactions with adhesion molecules on the endothelial cell surface, migration of T-cells into the skin and activation of T-cells – by inhibiting the binding of LFA-1 to ICAM-1.

Efalizumab was codeveloped by Xoma and Genentech and licensed to Serono for marketing worldwide outside the U.S. and Japan. Genentech and Xoma retain U.S. development and marketing rights and Genentech holds exclusive marketing rights in Japan. A BLA was submitted by Xoma in the U.S. in December 2002 and Serono filed an MAA with the EMEA for the treatment of adults with moderate to severe plaque psoriasis earlier this year. The applications are supported by efficacy and safety data from more than 2,100 patients with psoriasis treated with efalizumab as a once-weekly s.c. injection in phase III studies. Patients treated with efalizumab demonstrated fast onset of clinical response (as early as 2 weeks) and control of plaque psoriasis over a 1-year treatment period. Serono plans to submit marketing authorization applications in Canada, Australia and Switzerland by the end of the first quarter. The MAb is also in phase II testing for rheumatoid arthritis and psoriatic arthritis, and additional autoimmune indications are being explored (1-9).

An open-label, multicenter, dose-escalating phase I/II study including 39 patients with moderate to severe psoriasis assessed the efficacy of efalizumab in the treatment of T-cell-mediated diseases. Treatment of the patients with different efalizumab doses and schedules revealed a clinical, histological and pharmacokinetic dose-response relationship. The mean decrease in the PASI score induced by efalizumab varied from 10% to 47% depending on the specific dose and schedule administered to the patients. The drug also decreased epidermal and dermal T-cell counts, epidermal thickness, and ICAM-1 and keratin 16 (K16) expression, and adverse effects were tolerable. The authors concluded that substantial disease improvement required administration of efalizumab at doses of at least 0.3 mg/kg weekly (10).

The mechanism of action of efalizumab was investigated using skin lesion biopsies from 13 patients with psoriasis vulgaris treated with 2 mg/kg/week s.c. for 12 weeks. The effects on T-cell infiltration into the skin and on the expression of type 1 inflammation-related genes were compared in complete responders (6 patients) and incomplete responders (7 patients). Although a similar decrease in T-cell infiltration (57% *vs*. 47%) was observed in complete and incomplete responders, significantly greater reductions in acanthosis (73% *vs*. 19%) and K16 mRNA (10-fold *vs*. 3-fold) were obtained in complete compared to incomplete responders. Significant reductions in type 1 inflammation-related genes were seen in complete responders, with 85%, 94%, 64% and 61% mean reductions, respectively, in IL-8, iNOS, IL-12 and interferon gamma mRNA. Again, incomplete responders showed smaller reductions in these parameters. Clinical improvement was correlated to a much greater extent with reductions in inflammation-related genes than with reductions in T-cell numbers. Thus, the therapeutic efficacy of efalizumab appears to involve suppression of disease-related genes, independent of its effect on T-cell migration (11).

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5. *Serono's Raptiva marketing rights extended to Asia*. DailyDrugNews.com (Daily Essentials) Feb 10, 2003.

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

## Etanercept

Etanercept (Enbrel®) is a fully human anti-TNF therapy currently approved and marketed for reducing the signs and symptoms and inhibiting the progression of structural damage in patients with moderately to severely active rheumatoid arthritis, as well as to reduce the signs and symptoms of moderately to severely active polyarticular-course juvenile rheumatoid arthritis. During 2002, the biologic was also cleared for psoriatic arthritis in the E.U. and the U.S. A supplemental BLA for ankylosing spondylitis has been granted priority review by the FDA. Etanercept is also in phase III evaluation for psoriasis and Amgen expects to file for regulatory approval for this indication this year. Discovered by Immunex, now part of Amgen, etanercept was jointly developed and is copromoted in North America by Amgen and Wyeth; Wyeth affiliates market it outside North America (1).

The efficacy of long-term therapy with etanercept was assessed in 10 patients with severe psoriatic arthritis resistant to disease-modifying antirheumatic drugs (DMARDs). Eight of 10 patients remained on treatment after 2 years and were receiving 25 mg of etanercept s.c. twice weekly or once every 10 days, with or without additional DMARDs. Compared to after 1 year of treatment, the patients showed further improvements in disease activity, number of swollen joints and pain scores (2). The results of this study and some that follow are summarized in Table II.

A retrospective analysis of data from 66 patients with rheumatoid arthritis or psoriatic arthritis revealed that treatment of fibromyalgia and sleep disturbances improved the efficacy of etanercept treatment. The use of other medications was also reduced when fibromyalgia and sleep disturbances were improved (3).

A phase II clinical trial randomized 60 patients with psoriatic arthritis to receive either etanercept 25 mg s.c. twice weekly or placebo for 12 weeks. At the end of the treatment, 87% of patients treated with etanercept and 23% of those who received placebo showed clinical improvement. The median improvement in the psoriatic symptoms was estimated to be 46% with etanercept and 9% with placebo (4).

A multicenter, double-blind phase III clinical trial compared the effects of etanercept 25 mg s.c. twice weekly and placebo in 205 patients with psoriatic arthritis. After treatment for 24 weeks, the median improvement in target lesion was estimated to be 33% in etanercept-treated patients and 0% in placebo-treated patients. Significant differences were also found in the median improvement in the PASI score of the patients (47% with etanercept *vs.* 0% with placebo). Both etanercept and placebo were well tolerated. Assessment by various measures also showed that etanercept significantly improved health-related quality of life over placebo (5-8). The possible interference of etanercept with the immune system was also assessed in this trial. No significant differences were found between etanercept-treated and placebo-treated patients in the immunological response induced after injection of a pneumococcal vaccine. Concomitant treatment with methotrexate was found to reduce the patients' antibody response to challenge with the pneumococcal vaccine (9). Patients enrolled in this trial continued treatment in a 1-year, open-label extension. Review of radiographs of the hands and wrists of the patients showed that those treated with etanercept had significantly less disease progression compared with those given placebo (10).

Patients with psoriasis (n=112) included in a multicenter, double-blind trial were randomized to s.c. placebo or etanercept 25 mg given twice weekly for 24 weeks. At 12 weeks, 30% of etanercept-treated patients achieved at least 75% improvement in the PASI score, compared with 2% in the placebo group. Efficacy increased with longer treatment and the drug was well tolerated. Etanercept was also more effective than placebo in improving several lesion assessment scores and health-related quality of life (11-14).

Etanercept increased treatment efficacy without increasing toxicity in 6 patients with severe, resistant psoriasis (3 also having psoriatic arthritis) already receiving systemic therapy, phototherapy and/or topical therapy (15).

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

| Indication | Design | Treatments | n | Conclusions | Ref. |
|---|---|---|---|---|---|
| Psoriatic arthritis | Open | Etanercept, 25 mg sc 2x/wk x 2 y (n=4)<br>Etanercept, 25 mg sc 1x/10 d x 2 y (n=2) | 10 | Etanercept showed a satisfactory and sustained response in patients with severe, resistant psoriatic arthritis. In some patients the frequency of injections was decreased with continued efficacy, which could reduce the cost and potential adverse events | 2 |
| Psoriatic arthritis | Pooled/meta-analysis | Phase II trial in psoriatic arthritis:<br>Etanercept, 25 mg sc 2x/wk + Background NSAIDs x 12 wk → Etanercept, 25 mg sc 2x/wk x 6 mo (n=30)<br>Placebo + Background NSAIDs → Etanercept, 25 mg sc 2x/wk x 6 mo (n=30)<br>Phase II trial with no psoriatic arthritis:<br>Etanercept, 25 mg sc 2x/wk x 24 wk (n=57)<br>Placebo (n=55)<br>Phase III trial:<br>Etanercept, 25 mg sc 2x/wk x 24 wk (n=101)<br>Placebo (n=104) | 407 | Etanercept administered subcutaneously at a dose of 25 mg twice weekly was effective and well tolerated in patients suffering from psoriasis with or without psoriatic arthritis | 4 |
| Psoriatic arthritis | Randomized, double-blind, multicenter | Etanercept, 25 mg sc 2x/wk x 6 mo<br>Placebo | 205 | Etanercept was well tolerated and effective in improving health-related quality of life in patients with psoriatic arthritis | 8 |
| Psoriatic arthritis | Randomized, multicenter | Etanercept x 4 wk → Etanercept + Pneumococcal vaccine<br>Etanercept x 4 wk → Etanercept + Methotrexate + Pneumococcal vaccine<br>Placebo x 4 wk → Etanercept + Pneumococcal vaccine<br>Placebo x 4 wk → Etanercept + Methotrexate + Pneumococcal vaccine | 184 | Previous treatment with etanercept did not affect the response to pneumococcal vaccination, although methotrexate had a notable impact on the immune response in patients with psoriatic arthritis | 9 |
| Psoriasis | Randomized, double-blind, multicenter | Etanercept, 25 mg sc 2x/wk x 24 wk (n=57)<br>Placebo (n=55) | 112 | Compared with placebo, etanercept significantly increased the percentage of psoriatic patients who showed at least 75% improvement in symptom score after 12 and 24 weeks of treatment. This improvement was associated with a greater decrease in epidermal thickness | 12, 14 |

Positive results were reported from a phase III trial of etanercept in the treatment of moderate to severe plaque psoriasis. The trial met the primary and secondary endpoints. Nearly half of the patients showed a rapid and significant response to treatment with etanercept, with at least a 75% improvement in their PASI score after 12 weeks. Patients continued to show improvement over the entire treatment period, nearly 60% of patients achieving this endpoint after 24 weeks. A second phase III study is under way (16).

In a population of 10 children with chronic juvenile dermatomyositis, the addition of etanercept (0.4 mg/kg s.c. twice weekly) to background medication for 12 weeks was well tolerated and significantly improved the muscle and cutaneous manifestations of the disease (17).

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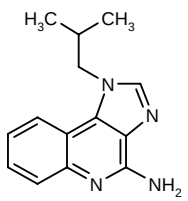
*Original monograph* - Drugs Fut 1998, 23(9): 951.

## Imiquimod




Topical imiquimod (Aldara™ 5% cream), the first in a new class of drugs known as immune response modifiers (IRMs), is currently approved and marketed by 3M Pharmaceuticals in over 40 countries for the treatment of external genital and perianal warts. The IRM is also being evaluated in clinical trials for actinic keratosis (AK) and superficial basal cell carcinoma (BCC). Phase III trials for both of these new indications are under way, with regulatory filings expected later this year.

Positive results have been reported by 3M from pivotal phase III studies of imiquimod 5% cream for multiple AKs and BCC. In 2 double-blind, randomized, vehicle-controlled trials, 436 patients with multiple AKs received imiquimod or vehicle cream twice a week for 16 weeks. At 8 weeks posttreatment, the median reduction in number of AK lesions counted at baseline was 83% in the imiquimod group compared to 0% in the placebo group. Complete clearance was seen in 45% of imiquimod patients compared to 3% of placebo patients. For BCC, 2 double-blind, randomized, placebo-controlled trials were conducted in 724 patients who received imiquimod or vehicle cream once daily, 5 or 7 times per week for 6 weeks. Optimal dosing was 5 times per week, with a histological clearance rate of 82% compared to 3% with placebo (1).

Topical imiquimod 5% cream administered 3 times a week for 8 weeks or 5 times a week for 5 weeks was effective in the treatment of viral and oncological dermatoses (BCC, AK or molluscum contagiosum) in chronically immunosuppressed transplant patients (2). The results of this study and some that follow are summarized in Table III.

The efficacy of imiquimod 5% cream in the treatment of verrucae vulgaris may be improved by combining it with keratolytics, cryotherapy or occlusion. Currently available evidence suggests that topical imiquimod may be effective in several dermatoses, including nongenital human papillomavirus warts, herpes simplex, molluscum contagiosum, AK, and basal and squamous cell carcinoma (3).

Seven patients with AKs of the face and head received topical imiquimod 5% cream 2-3 times a week for a total of 8 weeks. The treatment was well tolerated and successfully cleared all actinic lesions, with no recurrences reported throughout the follow-up period (4).

Imiquimod cream almost completely resolved AKs in a patient who applied the cream 3 times per week for 4 weeks. Two other patients applied imiquimod cream 2-3 times per week for 8 weeks and then twice weekly for 9 months, resulting in substantial reductions in AKs. Local inflammation in these patients was controlled with reductions in dosing (5).

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

| Indication | Design | Treatments | n | Conclusions | Ref. |
|---|---|---|---|---|---|
| Basal cell carcinoma, actinic keratosis, molluscum contagiosum | Open | Imiquimod 5% cream top 3x/wk x 8 wk<br>Imiquimod 5% cream top 5x/wk x 5 wk | | Imiquimod 5% cream was effective and well tolerated in the treatment of specific viral and oncological dermatoses in immunosuppressed transplant patients | 2 |
| Actinic keratosis | Open | Imiquimod 5% cream top 2x/wk x 8 wk<br>Imiquimod 5% cream top 3x/wk x 8 wk | 7 | Imiquimod 5% cream was effective and well tolerated in the treatment of actinic keratosis | 4 |
| Actinic keratosis | Open | Imiquimod 5% cream, od 3x/wk x 4 wk [in 8-wk cycles, max 3 cycles allowed] | 25 | Imiquimod 5% cream was highly efficacious and well tolerated, leading to a high level of treatment compliance | 7 |
| Actinic keratosis | Randomized, double-blind | Imiquimod 5% top 3x/wk x 12 [max.] wk (n=34)<br>Placebo (vehicle) (n=18) | 36 | Despite causing frequent mild to moderate adverse effects, imiquimod was well tolerated and all patients completed 12 weeks of therapy with no adverse event-related withdrawal. Imiquimod was thus an effective and well tolerated treatment for actinic keratosis | 8 |
| Basal cell carcinoma | Open | Imiquimod 5% cream top 5x/wk x 12 wk | 24 | Imiquimod 5% cream was safe and effective in the treatment of patients with basal cell carcinoma | 12 |
| Basal cell carcinoma | Pooled/meta-analysis | Imiquimod 5% cream, top od 2x/wk x 6 wk [+ occlusion] (n=43)<br>Imiquimod 5% cream, top od 2x/wk x 6 wk [without occlusion] (n=45)<br>Imiquimod 5% cream, top od 3x/wk x 6 wk [+ occlusion] (n=46)<br>Imiquimod 5% cream, top od 3x/wk x 6 wk [without occlusion] (n=49) | 183 | Imiquimod 5% cream with or without occlusion was safe and effective in the treatment of basal cell carcinoma | 13 |
| Basal cell carcinoma | Pooled/meta-analysis | Imiquimod, top od 3x/wk x 6 wk (n=32)<br>Imiquimod, top bid 3x/wk x 6 wk (n=31)<br>Imiquimod, top od 7x/wk x 6 wk (n=35)<br>Imiquimod, top bid 7x/wk x 6 wk (n=1)<br>Imiquimod, top od 3x/wk x 12 wk (n=20)<br>Imiquimod, top od 5x/wk x 12 wk (n=23)<br>Imiquimod, top od 7x/wk x 12 wk (n=21)<br>Imiquimod, top bid 7x/wk x 12 wk (n=4)<br>Placebo (n=24) | 191 | Imiquimod 5% cream was well tolerated and especially effective in patients with nodular basal cell carcinoma when administered once daily 7 days/week for 6 or 12 weeks | 14 |
| Basal cell carcinoma | Open | Imiquimod 5% cream top 5x/wk | 6 | Topical application of imiquimod 5% cream increased the susceptibility of basal cell carcinoma to pro-apoptotic signals and activated the antitumor immune response | 15 |
| Basal cell carcinoma | Double-blind | Imiquimod 5% cream top 5x/wk x 2 wk (n=24)<br>Imiquimod 5% cream top 5x/wk x 4 wk (n=24)<br>Imiquimod 5% cream top 5x/wk x 6 wk (n=24) | 72 | Compared to once-daily administration, imiquimod 5% cream 5 times weekly was equally effective and was associated with less inflammation in treating basal cell carcinoma and reducing tumor burden before surgery | 17 |
| Vulval cancer | Open | Imiquimod, top od 1x/wk x 16 wk (n=6)<br>Imiquimod, top od 2x/wk x 16 wk (n=5)<br>Imiquimod, top od 3x/wk x 16 wk (n=2) | 13 | Topically applied imiquimod 5% cream showed evidence of efficacy and was mainly associated with local adverse effects in patients with vulval intraepithelial neoplasia | 20 |

*Continuation*

*Table III (Cont.): Clinical studies of imiquimod (from Prous Science Integrity®).*

| Indication | Design | Treatments | n | Conclusions | Ref. |
|---|---|---|---|---|---|
| Vaginal cancer | Open | Imiquimod 5% cream intravag od 3x/wk x 8 wk | 3 | Intravaginal application of imiquimod 5% cream was well tolerated and induced regression of disease by at least two severity grades in women with high-grade vaginal intraepithelial neoplasia | 21 |
| Metastatic melanoma | Open | Imiquimod 5% cream, top od 3x/wk x 4 mo | | Topical administration of imiquimod 5% cream was well tolerated and induced complete clearing of metastatic skin lesions | 22 |
| Metastatic melanoma | Open | Imiquimod 5% cream, 37.5 mg top bid x 18 wk (n=1)<br>Imiquimod 5% cream, 50 mg top bid x 28 wk (n=1)<br>Imiquimod 5% cream, 25 mg top bid x 4 wk → IL-2, 3x/wk + Imiquimod 5% cream, 25 mg top bid x 2 wk → Imiquimod 5% cream, 25 mg top bid x 4 wk (n=1) | 3 | Imiquimod 5% cream was effective in clearing most metastatic skin lesions of patients with malignant melanoma, although in 1 case the treatment had to be supplemented with IL-2. The therapy was well tolerated, as only mild adverse effects were reported | 23 |
| Genital warts | Open | Imiquimod 5% cream, top bid x 16 wk [max] (n=32)<br>Imiquimod 5% cream, top od x 16 wk [max] (n=32)<br>Imiquimod 5% cream, top 3x/wk x 16 wk [max] (n=26) | 90 | Topical imiquimod cream was effective and well tolerated in the treatment of women with genital warts | 26 |
| Genital warts | Open | Imiquimod 5% cream, top 6-12 h/d 3x/wk x 3 mo | 4 | Immune restoration obtained by highly active antiretroviral therapy resulted in better efficacy of imiquimod in the treatment of external anogenital warts in HIV-infected patients | 27 |
| Anal warts | Open | Imiquimod 5% cream top od x 3 mo | 48 | Imiquimod 5% cream anal tampons were effective and well tolerated in patients with intraanal condylomata acuminata | 29 |
| Anal and genital warts | Open | Imiquimod, 5% cream tid x 16 wk | 725 | Imiquimod 5% cream was effective and well tolerated in the treatment of anogenital warts in female patients; reapplication for recurrences was also safe | 30 |
| Genital warts | Open | Imiquimod 5% cream top od 2x/wk x 16 wk [extended to 32 wk if warts cleared partially after first treatment or if recurrence during follow-up] | 943 | Imiquimod 5% cream was safe and effective in the treatment of external genital/perianal warts | 32 |
| Cutaneous warts | Open | Imiquimod 5% cream, top bid x 5.8 [mean] mo | 18 | Topical administration of imiquimod 5% cream was effective and well tolerated in patients with refractory viral warts | 33 |
| Healthy volunteers | Pooled/meta-analysis | Imiquimod 5% cream top od<br>Placebo | | Imiquimod 5% cream was as safe as placebo and did not increase photocontact allergy, phototoxicity or photodamage when applied to normal skin before UV irradiation | 37 |
| Molluscum contagiosum | Open | Imiquimod 5% cream top od x 10 wk [or until lesions disappear] | 11 | Topical imiquimod 5% cream was effective and well tolerated in the treatment of children with molluscum contagiosum | 38 |

*Continuation*

*Table III (Cont.): Clinical studies of imiquimod (from Prous Science Integrity®).*

| Indication | Design | Treatments | n | Conclusions | Ref. |
|---|---|---|---|---|---|
| Herpes simplex | Randomized, double-blind | Imiquimod 5% cream, top 1x/wk x 3 wk (n=34)<br>Imiquimod 5% cream, top 2x/wk x 3 wk (n=32)<br>Imiquimod 5% cream, top 3x/wk x 3 wk (n=28)<br>Placebo (n=30) | 124 | Topical imiquimod 5% cream had no apparent effect on the short-term natural history of herpes genitalis recurrences | 41 |
| Hemangioma | Open | Imiquimod top od 3x/wk x 2 wk → No treatment x 2 wk → Imiquimod top 1x/2 d x 4 wk (n=1)<br>Imiquimod top od 3x/wk x 3 wk → No treatment x 2 mo → Imiquimod top 1x/2 d x 6 wk (n=1) | 2 | Imiquimod 5% cream was both safe and effective in the treatment of hemangioma in infants | 42 |

A 43-year-old Caucasian patient treated with immunosuppressants due to a prior renal transplant and multiple AKs on his arms was successfully treated with imiquimod 5% cream administered topically for 3 months (6).

A pilot study was conducted to evaluate imiquimod 5% cream as treatment for 25 patients with 5-20 AKs of the forehead, scalp and cheek. The cream was applied once daily, 3 times a week for 4 weeks, followed by no treatment for 4 weeks and resumption of treatment if necessary for a maximum of 3 cycles. Efficacy and tolerability led to a high level of treatment compliance in the study. Most (82%) of the anatomic sites were cleared of AKs, and 15 of 33 anatomic sites were clear by the end of the first cycle (7).

A randomized, double-blind study compared treatment of AK lesions with vehicle or imiquimod 5% cream 3 times weekly for a maximum of 12 weeks. Imiquimod cream successfully cleared the lesions of 21 of 25 patients and partially cleared the lesions of 2 others. After 1 year, recurrence was observed in 10% of imiquimod-treated patients. Imiquimod was well tolerated and was not associated with any withdrawals from the study (8).

In samples from 10 patients with BCC who were treated with imiquimod 5% cream or vehicle 5 times per week for up to 2 weeks, the CD95 receptor (Fas-R) was expressed on BCC cells in 3 of 4 BCCs treated with imiquimod but in none of the carcinomas treated with vehicle. Also, T-lymphocytes opposed to BCC cells were identified in all carcinomas treated with imiquimod and expressing Fas-R (9).

Topical application of imiquimod 5% cream once daily promoted the infiltration of immune cells into the lesions of 16 patients with BCC. The first cell types infiltrating the tumors were $CD4^+$ T-cells, macrophages and dendritic cells, followed later by $CD8^+$ T-cells. This suggested that the destruction of tumors enhanced by imiquimod takes place following an immune-mediated mechanism (10).

Patients with superficial and nodular BCC (n=24) applied imiquimod 5% cream b.i.d. 3 times per week in an 8-week study. Clinical and histological clearance was seen in 83.3% of patients at the end of the study. The treatment was well tolerated, with cutaneous reactions including pruritus, pain, eroded lesions and ulcers seen by week 2 in 63%, 13%, 42% and 13% of patients, respectively. Doses were reduced to once-daily application in 15% of patients (11).

An open-label clinical trial included 24 patients with BCC who were treated with imiquimod 5% cream once daily, 5 days a week for 12 weeks. All patients showed remission of the disease, which was complete in 58% and partial in the remaining 42%; no patients reported stable disease or progression. Most patients showed local skin reactions, including erythema, edema, vesicles, erosion and desquamation. These promising efficacy and safety results were maintained after follow-up of 3 months (12).

Two open-label studies compared the efficacy and safety of topical imiquimod 5% cream administered 2 or 3 times a week and without occlusion in 183 patients with superficial or nodular BCCs. The complete response rates measured after treatment for 6 weeks and a follow-up period of 6 additional weeks were higher when imiquimod was administered 3 days a week and was combined with occlusion (87% for superficial BCC and 65% for nodular disease). Occlusion had no significant effect on the antitumor efficacy of the treatment. The drug was safe and well tolerated; the most common adverse event consisted of application site reactions and the percentage of serious adverse events was consistently low (4.3% for superficial BCC and 4.2% for nodular disease) (13).

Two open-label phase II clinical trials were conducted to determine the efficacy and safety of imiquimod 5% cream in the treatment of nodular BCC. A total of 99 patients were randomized to receive the drug once or twice daily at dosing frequencies ranging from 3-7 times a week for 6 or 12 weeks. The highest clearance rates were obtained for topical imiquimod 5% cream once daily for 7 days a week: 71.4% and 76.2% for the 6- and 12-week treatments, respectively. Local skin reactions were the most common adverse events and overall the treatment was well tolerated (14).

A pilot study assessed the efficacy and safety of topical imiquimod 5% cream in 6 patients with BCC. Once-daily application of the cream 5 times a week decreased the expression of Bcl-2 in tumor cells (which may make them more sensitive to proapoptotic signals) and activated the immune system against the tumor (15).

Five patients with BCC received open treatment with imiquimod 5% cream applied 3 times per week for up to 16 weeks. Resolution of BCC, as well as local inflammation during therapy, were seen in all patients. No cases of recurrence were noted during follow-up of 5-13 months (16).

A double-blind, vehicle-controlled clinical trial assessed the efficacy and safety of imiquimod 5% cream in 72 patients with BCC. The patients were randomized to receive either imiquimod or vehicle 5 times a week for 2, 4 or 6 weeks. All dosing regimens were as effective as imiquimod once daily for 6 weeks in clearing the tumor or at least reducing tumor burden before surgery. The lower dose frequency was correlated with a decreased induction of inflammation and therefore with a better safety profile (17).

A brother and sister with xeroderma pigmentosum and facial BCCs which were developing faster than could be dealt with surgically were treated with imiquimod 5% cream. The cream was applied as often as tolerated. The treatment was effective, despite a severe inflammatory response in the sister, and reduced the rate of new tumor development (18).

A 55-year-old man with porokeratosis of Mibelli on the right leg was treated with imiquimod 5% cream 5 times a week for 3 months. This proved ineffective, but when the same treatment was combined with occlusion using an adhesive polythene dressing, the lesion became inflamed with erythema and induration within 3 weeks and was cleared after 2 more weeks. No recurrence was detected at follow-up 1 year later (19).

Fifteen patients with histologically confirmed vulval intraepithelial neoplasia were topically treated with imiquimod 5% cream once daily up to 3 times a week for a maximum of 16 weeks. Two patients discontinued the study, and the frequency of topical application of the cream in the remaining 13 patients was limited by local side effects such as soreness and burning. Two patients applied the cream 3 times weekly, 5 twice weekly and 6 once weekly. Four patients showed clinical response to the treatment, and the authors concluded that the use of measures aimed at alleviating the discomfort associated with adverse events might allow a more aggressive use of imiquimod, and hence improved clinical results (20).

Three women with high-grade vaginal intraepithelial neoplasia were treated with vaginal applications of imiquimod 5% cream 3 times a week for 8 weeks. The treatment induced regression of the neoplasia by at least two grades, and in 1 patient no histological evidence of the disease was found. The authors concluded that imiquimod 5% cream might be an alternative therapy for vaginal intraepithelial neoplasia (21).

Two patients with metastatic melanoma to the skin received topical imiquimod 5% cream 3 times a week. The treatment was highly effective, as it induced complete clearing of skin lesions in 1 of the patients after 4 months and in the other patient after 8 months. No residual melanoma cells were detected, and the only adverse effect associated with treatment was peritumoral erythema and superficial ulceration found in 1 patient (22).

Topical administration of imiquimod 5% cream twice daily for 6-8 h under occlusion was effective in clearing cutaneous metastases in 3 patients with malignant melanoma. Depending on the patients' response to the drug, the duration of treatment varied from 10-28 weeks. In 1 patient, intralesional injection of IL-2 (3 times weekly for 2 weeks) was necessary to induce a marked response to imiquimod. The only adverse effects associated with the drug were local skin reactions that included erythema, erosions and/or mild pruritus (23).

Investigators identified 15 patients with actinic cheilitis who had received treatment with imiquimod 5% cream 3 times per week for 4-6 weeks. A review of the records from these patients revealed that all achieved clearing of actinic cheilitis at 4 weeks after the end of therapy, although most experienced mild to moderate inflammation, local edema or both (24).

A 92-year-old woman with lentigo maligna on the left temporal region was treated with topical imiquimod 5% cream once daily. At 3 months, the patient developed severe inflammation and crusty lesions in the treated area, combined with granulomatous tissue and a reduction in the pigmented area. One week later, most of the treated area showed normal pigmentation and no signs of lentigo or lentigo maligna (25).

An open-label phase II clinical trial randomized 90 women with external genital warts to receive imiquimod 5% cream administered topically twice daily, once daily or 3 times weekly until baseline warts had cleared completely or for a maximum of 16 weeks. No significant differences were found among the clearance rates for all study groups. The 3-times-weekly dosing regimen showed the best safety profile, as this schedule was associated with a lower incidence of severe skin erythema, a lower number of patients requiring at least one rest period during treatment, and a lower percentage of missed doses due to rest periods (26).

Imiquimod 5% cream was used by 4 HIV-infected patients to treat recurring anogenital warts. Patients had achieved good control of HIV infection with HAART and applied imiquimod 3 times/week for a minimum of 3 months. The treatment produced irritation in 3 patients, which in 1 case was severe. One complete and 2 partial responses were seen initially; those with partial responses achieved clearance with more time or retreatment (27).

After ablation of perianal condyloma and anal canal condyloma, 10 male patients were treated with imiquimod-containing suppositories 3 times weekly for 3-4 months. The treatment was safe, cleared early local recurrences and all patients were without recurrences after 6-18 months of follow-up (28).

A study conducted in 48 patients assessed the potential use of imiquimod 5% anal tampons as an adjunct to surgery in the treatment of intraanal condylomata acuminata. Overnight application of the tampons for 3 months resulted in complete clearance of intraanal warts in 12 patients (25.0%), reduction in the number and size of warts in 16 patients (33.3%) and stable disease in 8 patients (16.7%). The treatment showed a good safety profile; the most common adverse event was mild local irritation and only 3 patients discontinued treatment (29).

Two open-label studies assessed treatment of 600 women with anogenital warts with imiquimod 5% cream

3 times/week for up to 16 weeks. The treatment was effective, leading to complete clearance in 75% of patients, and was safe during the study and during additional treatment for patients with incomplete clearance (30).

The records of 60 patients with anogenital warts who were treated with placebo or imiquimod 5% cream and underwent surgical excision of remaining warts were reviewed to assess the incidence of recurrence. The recurrence rate in patients with a complete response to imiquimod was 15%, in patients with surgical removal of residual warts after 16 weeks of imiquimod therapy it was 20%, and in those with no imiquimod treatment and surgical removal of warts only it was 65% (31).

A multicenter clinical trial evaluated the efficacy and safety of topical imiquimod 5% cream 3 times a week in 943 patients with external genital/perianal warts. The cream was applied for 16 weeks, or for 32 weeks in the event of partial clearing or recurrence of skin lesions. At the end of the treatment, the overall clearance rate was 65.5% and the recurrence rate was low (8.8% and 23.0% after follow-up for 3 and 6 months, respectively). Imiquimod also showed a good safety profile, with erythema being the most frequent adverse event reported by 67% of the patients (32).

Long-term topical administration of imiquimod 5% cream has proven effective in the treatment of children with cutaneous viral warts. From a group of 18 children who received imiquimod 5% cream twice a day for a mean of 5.8 months, 16 (88.9%) reported complete clearing of their warts and the remaining 2 showed improvement but were lost to follow-up. Only 2 patients showed recurrence of warts at 15 and 20 months after stopping treatment, and no severe or serious adverse events were reported during a mean follow-up of 20.8 months (33).

Topical administration of a cream containing 5% imiquimod once daily under occlusion for 4 weeks induced complete remission of nongenital warts in 8 of 10 patients enrolled in the study. Extension of the treatment for another 4 weeks resulted in complete remission of the warts in another patient, whereas the last patient did not respond to the drug. No wart recurrence was detected after follow-up for 3 months, and no adverse events were reported. Although expensive, the excellent cosmetic results and the possibility of self-application at home prompted researchers to suggest that administration of imiquimod 5% cream might become a standard therapy for nongenital warts in the future (34).

An erythematous plaque found on the forehead of a 74-year-old patient that had not responded to previous treatments was diagnosed as granuloma faciale. Topical administration of imiquimod 5% cream once daily for 14 days first increased inflammation in the treated area but then resulted in complete resolution of the lesion. No recurrence was detected after 9 months' follow-up (35).

An 83-year-old man with inoperable scrotal extramammary Paget's disease was successfully treated with topical application of imiquimod 5% cream twice daily for 8 weeks over a period of 3 months (36).

Three randomized, placebo-controlled clinical trials evaluated the safety of imiquimod 5% cream applied to normal white skin before ultraviolet radiation. No increase in photocontact allergy, phototoxicity or photodamage (assessed measuring sunburn cell counts and DNA pyrimidine dimer formation) was found for imiquimod compared to placebo (37).

Topical administration of imiquimod 5% cream once every night was effective in the treatment of 11 children with molluscum contagiosum. After 10 weeks of treatment, 7 patients showed complete clearing of the skin lesions whereas the other 4 patients had a 30-50% reduction in the number of lesions. The most common adverse event was local erythema, and no children discontinued treatment due to irritation or pain (38).

Imiquimod 5% cream applied daily for up to 12 weeks was successfully used to treat 5 patients with molluscum contagiosum. All lesions were cleared in 4 patients and all but 2 in 1 patient who received therapy for 8 weeks. It was concluded that imiquimod 5% cream may offer an effective alternative home-applied topical treatment for molluscum contagiosum (39).

After surgical excision of 13 keloids in 12 patients, imiquimod 5% cream was applied for 8 weeks. No recurrence was seen in 11 evaluable keloids at 24 weeks. Hyperpigmentation occurred in 63.3% of keloids, and 2 patients experienced mild irritation and superficial erosion which did not prevent participation in the study (40).

The efficacy and safety of imiquimod 5% cream in decreasing recurrence of herpes genitalis was evaluated in a randomized, double-blind, placebo-controlled trial in 124 patients who had at least 6 recurrences per year. Patients applied imiquimod or placebo creams to lesions 1, 2 or 3 times per week for 3 weeks for each recurrence during a 16-week period. During the study and during a 16-week follow-up period, no significant differences in the time to first recurrence or annualized recurrence rates were seen between placebo and imiquimod treatment groups (41).

Topical imiquimod 5% cream applied 3 times/week was used to successfully treat 2 infants, 7 and 4 months old, with hemangioma. The treatment led to regression and nearly complete regression, respectively, of the lesions without recurrence (42).

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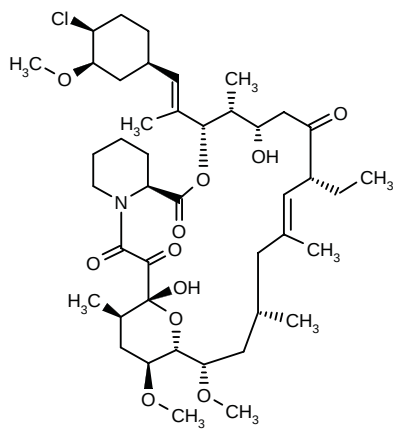
# Pimecrolimus



Pimecrolimus (SDZ-ASM-981, Elidel®) is a non-steroidal, skin-selective inflammatory cytokine inhibitor that was launched by Novartis in 2002 in the U.S. and Denmark in the form of a 1% cream for the treatment of atopic dermatitis (eczema).

Twelve other European countries – Austria, Belgium, Finland, France, Germany, Greece, Iceland, Italy, Luxembourg, Portugal, Spain and the U.K. – also agreed to approve pimecrolimus cream. Outside Europe and the U.S., it has been approved in Mexico, Venezuela, Colombia, Peru, New Zealand, Brazil and Kuwait, and applications have also been filed in Canada and Switzerland. The product is indicated for use in patients aged 2 years and over with mild to moderate disease, for the short-term treatment of signs and symptoms and intermittent long-term treatment for the prevention of the progression of flares. When used at the first signs of itching or redness of the skin, pimecrolimus has been shown in 1-year studies to prevent progression to severe flares in up to 57% of patients, and to eliminate the need for topical corticosteroid treatment in up to 64% of patients. The incidence of adverse events is low, the most common reported side effect in the pivotal efficacy studies being a mild to moderate temporary feeling of warmth or burning on the skin where the cream was applied. This occurred in fewer than 10% of children and in 10% of adults (1).

*In vitro* tests with human, porcine or rat skin revealed that pimecrolimus is 9-10 times less skin-permeable than tacrolimus, and 70-120 times less permeable than topical corticosteroids in the presence of a penetration enhancer (2).

The immunosuppressive properties of pimecrolimus were investigated in several *in vitro* tests, including the human mixed lymphocyte reaction, the measurement of histamine release from human basophils and the production of interferon γ and IL-4 from human peripheral blood mononuclear cells stimulated with CD3/CD28 and anti-CD3/CD28, respectively. In all of these tests, the $IC_{50}$ values were lower for pimecrolimus than for ciclosporin (3).

Contrary to corticosteroids, pimecrolimus induced no changes in the maturation of dendritic cells or the stimulation of T-cells *in vitro* and did not decrease the number of Langerhans cells after topical application to mouse skin (4).

Pimecrolimus was shown to be as effective as tacrolimus against allergic contact dermatitis in rats and mice, but had no effect on the subcutaneous lymphoid tissue, which decreased by 44% and 26% after a minimal effective dose of tacrolimus in mice and rats, respectively (5).

*In vivo* in rats, pimecrolimus (25 mg/kg p.o.) showed a higher affinity for skin than tacrolimus, and no accumulation of pimecrolimus was detected in skin after several oral doses (6).

The effects of pimecrolimus and tacrolimus in mice and rats were compared using a model of sensitization to oxazolone. Tacrolimus was reported to be at least 10 times more effective than pimecrolimus in inhibiting acute contact dermatitis in rats (7).

The results of a 1-year, randomized, double-blind, placebo-controlled trial in children with atopic eczema showed that treatment with pimecrolimus cream 1% improved parents' quality of life and childrens' health-related quality of life as compared to vehicle (8, 9).

Data from 250 infants enrolled in a 6-month study and from 711 children enrolled in a 1-year study of pimecrolimus treatment for atopic dermatitis were examined for evidence of a treatment effect on height and weight. No differences in height and weight were found between pimecrolimus- and vehicle-treated infants and children in these trials (10).

Twice-daily pimecrolimus 1% cream was compared to vehicle in two 6-week, multicenter, randomized studies enrolling children with atopic dermatitis. Pooled analysis of data from 403 patients showed that pimecrolimus acted rapidly and was significantly more effective than vehicle in improving Investigator's Global Assessment scores, Eczema Area and Severity Index and severity of pruritus scores (11). The results of this study and some that follow are given in Table IV.

In a multicenter, comparative, randomized, double-blind study, infants aged 3-23 months, children aged 2-17 years and adults receiving pimecrolimus (1% topical cream b.i.d. for 3 weeks over 12 months) for the treatment of mild to moderate atopic dermatitis all experienced a reduction in symptoms according to the Eczema Area and Severity Index. The drug was not only well tolerated and did not cause skin atrophy, but also reduced the number of eczematous flares and the level of pruritus after intermittent long-term use (12).

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

| Indication | Design | Treatments | n | Conclusions | Ref. |
|---|---|---|---|---|---|
| Atopic dermatitis | Randomized, double-blind, open, multicenter | Pimecrolimus 1% cream bid x 26 wk (n=267)<br>Placebo [vehicle] x 6 wk → Pimecrolimus 1% cream bid x 20 wk (n=136) | 403 | Pimecrolimus cream 1% was safe and effective as an alternative treatment for children and adolescents with atopic dermatitis | 11 |
| Atopic dermatitis | Randomized, double-blind | Pimecrolimus 1% cream, qid x 7 d → bid x 14 d<br>Pimecrolimus 1% cream, bid x 21 d | 49 | Both pimecrolimus 1% cream regimens were well tolerated and no difference between groups in the time to the onset of pruritus was seen | 14 |
| Atopic eczema | Pooled/meta-analysis | Pimecrolimus 1% cream x 6 wk<br>Placebo | 479 | Pimecrolimus 1% cream was effective in treating both Caucasian and non-Caucasian children with atopic eczema | 15 |
| Atopic eczema | Randomized, double-blind | Pimecrolimus 1% cream [at first signs or symptoms of atopic eczema] x 24 wk<br>Placebo [at first signs or symptoms of atopic eczema] x 24 wk | 100 | Pimecrolimus 1% cream was rapidly effective in reducing pruritus in patients with atopic eczema | 16 |

A randomized, double-blind, parallel-group study assessed the efficacy and safety of a regimen of pimecrolimus cream 1% q.i.d. for 7 days followed by b.i.d. dosing plus 2 additional doses for 14 days in 49 patients with atopic dermatitis. Both regimens were well tolerated, with a low incidence of adverse events and minimal levels of systemic exposure, and improved pruritus within 3-4 days of treatment (13, 14).

Pooled analysis of data from 3 double-blind, vehicle-controlled studies of pimecrolimus cream 1% in children with atopic eczema revealed that ethnic background did not affect the efficacy of the drug (15).

When administered to adult patients with atopic eczema, pimecrolimus cream 1% relieved itching and inflammation, prevented flare progression and reduced pruritus after only 3 days of treatment (16, 17).

An interim analysis of an open phase IV study (the NOBEL study) revealed that the good efficacy and safety of pimecrolimus cream 1% were paralleled by high patient satisfaction (18).

Adult atopic dermatitis patients (n=192) were randomized in a double-blind fashion to twice-daily treatment at the first signs or symptoms of atopic dermatitis with pimecrolimus-based treatment or conventional treatment in a 24-week study. The time to first flare was significantly longer in the pimecrolimus group (144 days *vs.* 26 days), and the mean improvement in quality of life was significantly greater in this group as well (23.8% *vs.* 22.0%). Safety was comparable between treatment groups (19).

A meta-analysis of two 1-year, randomized, double-blind studies evaluated treatment of pediatric patients with atopic dermatitis with pimecrolimus or conventional treatment. A total of 961 patients, aged 3 months to 17 years, were included and were treated with twice-daily pimecrolimus or vehicle at early signs or symptoms of disease. Significantly fewer flares were seen in patients applying pimecrolimus cream, regardless of initial disease severity (20).

Analysis of adverse events in a 1-year, multicenter, randomized, double-blind trial in 711 children with atopic dermatitis showed that the adverse event profile of patients given pimecrolimus who did not receive corticosteroids for control of disease flares was similar to that of those in the pimecrolimus treatment group given corticosteroids (21).

Pooled analysis of data from trials evaluating pimecrolimus cream treatment for atopic dermatitis in a total of 1,550 children showed that the incidence of application site burning was low and similar between patients treated with pimecrolimus and those in control groups (22).

Pooled analysis of data from 3 randomized, double-blind, vehicle-controlled, 6-week studies showed that the treatment of pediatric atopic dermatitis with pimecrolimus cream 1% was safe and effective. A total of 589 children aged 3 months to 17 years were included in the studies, in which pimecrolimus was well tolerated and cleared disease in 41% of patients as compared to 20% given vehicle (23).

Pimecrolimus or placebo was administered to 50 patients with psoriasis in a randomized, double-blind phase I/II study. Pimecrolimus 20 and 30 mg b.i.d. given for 4 weeks reduced PASI scores by 60% and 75%, respectively. The active treatment was well tolerated, and a gene profile was identified which is indicative of antiinflammatory activity without toxicity (24).

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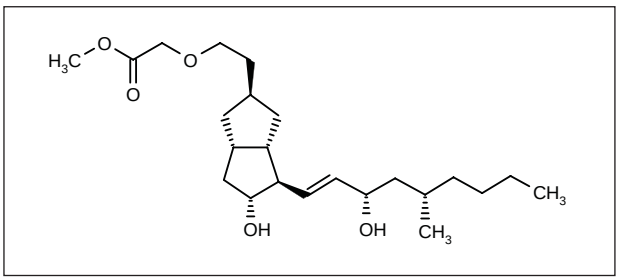
*Original monograph* - Drugs Fut 1998, 23(5): 508.

## Pimilprost




Pimilprost (SM-10902, Skipron™), a stable prostacyclin analogue developed as a wound-healing agent by Sumitomo Pharmaceuticals, is still under regulatory review in Japan for the treatment of skin ulcers (1).

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*Original monograph* - Drugs Fut 1996, 21(4): 369.

## Siplizumab

Siplizumab (MEDI-507) is an anti-T-cell monoclonal antibody that appears to selectively suppress the immune system by binding to CD2, a specific receptor found on T-cells and NK cells.

Under a research and license agreement dating from 1993, BioTransplant received exclusive rights from the Catholic University of Louvain to develop and commercialize the BTI-322 rodent monoclonal antibody, and subsequently sublicensed BTI-322 and its humanized analogue siplizumab to MedImmune, which is currently conducting phase II clinical trials for the treatment of psoriasis. MedImmune is also studying siplizumab for psoriatic arthritis and T-cell lymphoma. Siplizumab is an important component of BioTransplant's AlloMune™ System (see ref. 6) and the company has sublicensed its rights to develop the antibody as part of a xenotransplantation system to its joint venture with Novartis. The Catholic University of Louvain and BioTransplant are currently attempting to resolve a dispute relating to their original agreement. The university informed the company early this year of its intention to terminate the agreement and rights and licenses granted to BioTransplant, asserting that the latter had breached their agreement (1-3).

Intravenous administration of siplizumab for psoriasis was investigated in a single-dose, open-label phase I safety study in 14 patients and in a multiple-dose, open-label, dose-escalation phase I/II study in 26 patients. Doses above 1.2 mcg/kg produced significant disease responses, and the highest dose tested (40 μg/kg) was the most effective. Adverse events were largely mild to moderate and transient (4).

An open, dose-escalation phase I/II study evaluated treatment of psoriasis with siplizumab 0.1-7 mg given in weekly s.c. injections. Multiple injections produced reductions in disease severity scores, especially at the higher doses of siplizumab. The agent was well tolerated, with most adverse events being mild and transient (5).

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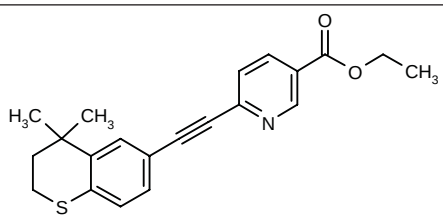
*Original monograph* - Drugs Fut 2002, 27(6): 558.

## Tazarotene




The topical receptor-selective retinoid tazarotene (AGN-190168) is currently used in the form of cream and gel for the treatment of psoriasis and acne, and an oral formulation is in late-stage development. In October of last year, the U.S. FDA additionally approved its use as an adjunctive agent in the topical treatment of facial fine wrinkling, mottled hypo- and hyperpigmentation, and benign facial lentigines in patients using a comprehensive skin care and sunlight avoidance program. In the U.S., tazarotene is marketed by Allergan under the brand name Tazorac® for psoriasis and acne, and it will be introduced as Avage™ for photodamage. Bioglan Pharma and Allergan market the drug in certain European and other markets as Zorac®. Tazarotene is also reportedly in late-stage development for certain cancers.

A total of 181 patients with moderate to severe plaque psoriasis were randomized to receive either placebo or an oral dose of tazarotene (0.4, 0.6, 0.8 or 1.1 mg) once daily for 12 weeks. This was followed by three 12-week open-label treatment periods during which each patient was successively treated with daily oral doses of 2.1-2.8, 4.2 and finally 6.3 mg tazarotene. Compared to placebo, a dose of 4.2 mg was associated with a higher rate of clinical success (79% *vs.* 24%), a higher rate of treatment success (86% *vs.* 20%) and a greater reduction in affected body surface area (17% *vs.* 3%). The safety profile of tazarotene was good, although it increased the incidence of cheilitis at doses above 2.8 mg/day (1).

Two clinical trials revealed that oral administration of tazarotene 4.2 or 6.3 mg once daily for 12 weeks had a reasonable safety profile and significantly improved the symptom scores for plaque elevation, erythema and scaling in patients with moderate to severe plaque psoriasis (2).

Two multicenter, double-blind clinical trials randomized 1,131 patients with photodamaged skin to receive either vehicle cream or tazarotene 0.1% cream once daily

for 24 weeks, followed by open-label administration of the drug to both study groups for another 28 weeks. Tazarotene was effective in improving the symptoms of photodamaged skin, including wrinkling, mottled hyperpigmentation, lentigines, irregular depigmentation, pore size and elastosis, and was well tolerated. Local skin irritation was especially evident during the first weeks of treatment, and tolerability gradually improved during the study (3, 4).

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*Original monograph* - Drugs Fut 1997, 22(3): 249.