

New products

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Elidel (pimecrolimus) cream 1%: A nonsteroidal topical agent for the treatment of atopic dermatitis

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Elidel is a steroid-free cream containing a 1% strength of the topical immunomodulator pimecrolimus. Elidel was specifically developed as a treatment for atopic dermatitis (AD) and is approved for use in children as young as 2 years of age. The production of inflammatory cytokines by activated T cells in skin is thought to play an important role in the pathogenesis of AD. Elidel potently suppresses cytokine production by dermal T cells without significantly impairing systemic immune responses. Elidel does not cause steroid-associated local effects, such as dermal atrophy, striae, or telangiectasia. In randomized controlled clinical studies, twice-daily application of Elidel was shown to significantly improve the signs and symptoms of AD in infants, children, and adults. The clinical effect of Elidel on pruritus, the most troublesome symptom of AD, can be observed within 1 week of therapy and is maintained for the duration of treatment. Elidel is well tolerated; the risk of application-site reactions, such as itching or burning, is comparable with that of the vehicle. Adverse effects were generally mild in patients receiving Elidel and occurred at rates comparable with those in patients receiving vehicle treatment. In a 1-year study, Elidel significantly reduced the incidence of flares when used at the first signs and symptoms of acute AD. As a result, overall corticosteroid use to treat flares was significantly lower in patients using Elidel for early intervention. (*J Allergy Clin Immunol* 2003;111:1153-68)

Key words: Atopic dermatitis, pruritus, corticosteroid, topical immunomodulator, eczema, cytokines, ascomycin, pimecrolimus, Elidel, inflammation, T cells

Atopic dermatitis (AD) is a chronic and inflammatory skin disorder characterized by erythematous, eczematous, and highly pruritic lesions. Onset is usually in early

Abbreviations used

ACD: Allergic contact dermatitis
AD: Atopic dermatitis
AUC: Area under the curve
BSA: Body surface area
EASI: Eczema Area and Severity Index
IGA: Investigator's Global Assessment
LOQ: Limit of quantitation

childhood, with only approximately 10% of patients presenting after 5 years of age.¹ Although a significant number of cases resolve or improve by adolescence, AD often persists into adulthood. In general, advancement of the disease from infancy to adulthood is characterized by a transition from acute, eczematous, and often exudative lesions to chronic skin changes, such as hyperpigmentation or hypopigmentation, lichenification, and generalized dryness.^{2,3} Hand dermatitis is a common finding in adults with a history of AD.⁴ Not only the appearance but also the location of AD lesions changes with age in a characteristic manner. Infantile AD involves the extensor surfaces of the extremities and the face, trunk, and neck areas.⁵ In chronic childhood and adult AD, the flexural surfaces of the extremities usually become involved. Pruritus is a prominent feature of AD at all stages and is the most troublesome of its symptoms for patients, as well as for their families and physicians.⁶ Scratching exacerbates inflammation and contributes to the chronic features of the disease,⁷ making control of pruritus an essential element of every AD treatment strategy.

Epidemiologic studies indicate that the worldwide incidence of AD has increased in recent decades, especially in industrialized countries.⁸ In the United States, AD has become a common condition in children, with a prevalence of anywhere from 7% to 17.2% in Oregon on the basis of a recent survey of 5- to 9-year-old children in that state.⁹ A study of eighth-grade children in Denmark found that more than one fifth had AD at some point in their lives and that the condition persisted into adolescence for a significant number.¹⁰

AD appears primarily to be a disease of immune dysfunction with a heritable component.¹⁰⁻¹² Among commonly observed immunoregulatory abnormalities in AD

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are increased levels of circulating IgE¹¹ and increased histamine release from basophils.¹³ Central to the pathogenesis of AD are hyperreactive cutaneous T cells, which secrete proinflammatory cytokines.¹⁴⁻¹⁶ The pivotal role of T-cell activity in the inflammatory process suggests that their activation might serve as an important therapeutic target in AD treatment.

The secretion of cytokines by cutaneous T cells orchestrates the inflammatory process. The T_H2 subtype predominates in acute lesions, as evidenced by high concentrations of IL-4 and IL-5 and low concentrations of IFN- γ , the latter being secreted primarily by T_H1 cells.¹⁷ As inflammation becomes chronic, a mixture of both T_H1- and T_H2-specific cytokines is observed.¹⁸ The mechanism of the cytokine switch from a predominantly T_H2 immune response to one governed by the mixture of T_H1 and T_H2 cells is still poorly understood but is thought to be driven in part by IL-12 production from monocytes-macrophages or from eosinophils within the lesion.¹⁸ IL-5 likely plays an important role in this process by prolonging the survival and function of infiltrating eosinophils.^{19,20} The transition to chronic AD is accompanied by the clinical changes of lichenification, epidermal hyperplasia, and dermal fibrosis.¹⁷

THE ATOPIC TRIAD

In many individuals, dermatitis occurs as one element of the atopic triad, which also includes asthma and allergic rhinitis.¹⁰ Although the role of food and aeroallergens in AD has been the subject of considerable debate and establishing a causal link between exposure to such allergens and AD has been difficult, immediate skin test reactivity to allergens, in addition to circulating IgE antibodies against airborne, food, or even microbial antigens, is a frequent finding.¹ The ability of these allergens to induce an eczematous lesion that clinically and histologically resembles *de novo* disease after epicutaneous application provides further evidence that AD can, in some cases, be driven by allergen contact with skin.²¹ The induced skin reaction is thought to be the end result of allergen binding to IgE-bearing epidermal Langerhans cells in sensitized individuals, with subsequent antigen presentation to T cells. Therefore at the present time, evidence supports the contention that the underlying immune deficits that give rise to atopic diseases overlap considerably. However, it is only in some sensitized individuals that symptoms of dermatitis are as clearly and significantly induced by allergen exposure as they are in allergic rhinitis and asthma.²²

MANAGEMENT OF AD: CURRENT STRATEGIES

The goals of AD treatment are to alleviate symptoms and reduce cutaneous inflammation. Identification and elimination of irritants, such as soaps, detergents, chemicals, and abrasives, can be helpful, as can elimination of specific foods and other allergens when these can be identified. Hydration of the skin through proper bathing

techniques and the frequent use of moisturizers reduces the symptom of dryness and is thought to help restore the integrity of the epithelial barrier.²³

To date, topical corticosteroids have been the mainstay of drug therapy for AD because of their broad immunosuppressant and anti-inflammatory effects.⁵ However, topical steroids have been associated with adverse local effects, such as dermal atrophy, acneiform eruption, striae, and telangiectasia, as well as a risk of systemic effects, such as hypothalamic-pituitary-adrenal axis suppression.²⁴⁻²⁸ These concerns have called into question the suitability of prolonged topical corticosteroid therapy, especially for children. In a recently published survey, patients with AD and their caregivers expressed concerns about the use of topical corticosteroids. Almost three quarters of those surveyed worried about using topical steroids on their own or their children's skin.²⁹ A significant number said they had been noncompliant with treatment because of these worries.

The concern about possible adverse steroid effects is one element of what appears to be a relatively high degree of dissatisfaction with traditional treatment modalities for AD on the part of physicians, as well as patients. A series of surveys conducted by the National Eczema Association for Science and Education found that almost 40% of physicians were not satisfied with the products available for treating AD.³⁰ The most common reasons for dissatisfaction were lack of efficacy and side effects, with the latter including local effects, such as skin atrophy and striae. Among patients, more than half of those surveyed expressed a low level of satisfaction with their care. These concerns have stimulated a search for nonsteroidal alternatives that can safely and selectively suppress the immune abnormalities that give rise to AD.

Cyclosporin A, originally developed as an immunosuppressant to prevent organ transplant rejection, inhibits T-cell activation and has shown activity against AD.³¹ Cyclosporin A is not active topically, and its oral administration is associated with a risk of serious systemic effects, particularly renal toxicity.³² The lack of topical efficacy of cyclosporin A might be due to its large molecular size, which impedes its ability to penetrate skin.³³ Tacrolimus (FK 506) is another potent immunosuppressant used to prevent graft rejection.³⁴ Tacrolimus, however, is active topically and has shown success in clinical trials for the treatment of AD.³⁵⁻³⁷ It has been marketed for patients with moderate-to-severe AD since early 2001 by Fujisawa Healthcare Inc as Protopic ointment (0.03% and 0.1% for patients ≥ 2 years and >15 years, respectively).³⁸⁻⁴⁰

ELIDEL'S MECHANISM OF ACTION

Unlike FK 506 and cyclosporin A, the ascomycin derivative pimecrolimus was developed specifically to treat inflammatory skin conditions.⁴¹ Pimecrolimus was the product of a research effort that sought to identify a compound with topical anti-inflammatory activity that did not impair natural systemic immunity.⁴² Pimecrolimus was one of 400 ascomycin derivatives screened and was select-

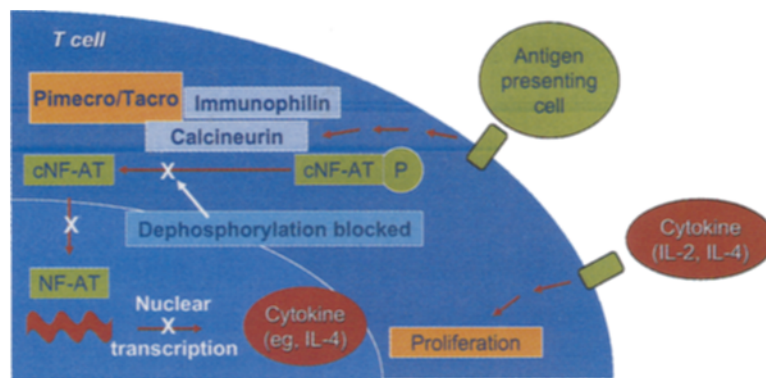


FIG 1. Macrolactams block inflammatory cytokine transcription in activated T cells.

ed for further development on the basis of its apparent skin-selective pharmacologic activities and favorable safety profile. Pimecrolimus is the active agent of Elidel Cream 1% (Novartis Pharmaceuticals), a formulation recently approved by the Food and Drug Administration for use in patients 2 years of age or older with mild-to-moderate AD.⁴³ Pimecrolimus binds with high affinity to macrophilin 12, and the complex is a potent inhibitor of the calcium-dependent phosphatase calcineurin.^{43,44} As a result, calcineurin-dependent transcription of early cytokine genes necessary for T-cell activation is blocked (Fig 1). By this means, pimecrolimus inhibits expression of a variety of cytokines, including the T_H2 -type cytokines IL-4 and IL-10 and the T_H1 -type cytokines IL-2 and IFN- γ .⁴⁴ Pimecrolimus also prevents the release of inflammatory cytokines and preformed mediators from mast cells *in vitro* after stimulation by antigen-IgE.⁴⁵ Therefore the clinical effects of pimecrolimus are thought to result from its inhibition of the release of cytokines and other proinflammatory mediators from T cells, basophils, and mast cells. By this means, pimecrolimus-containing Elidel cream is thought to block the cutaneous inflammatory process central to the pathogenesis of AD.

Preclinical studies

Preclinical studies in animal models have found that although pimecrolimus exhibits high anti-inflammatory activity in skin, it has only a low potential for systemic immunosuppression.⁴⁶ In a porcine model of allergic contact dermatitis (ACD), topical pimecrolimus was as effective as highly potent topical corticosteroids in inhibiting the intensity and extent of erythema and induration 1 day after antigen challenge in sensitized animals.⁴¹ Similarly, 3 rat models of systemic immunosuppression were used to compare the ability of pimecrolimus to (1) inhibit a localized graft-versus-host reaction, (2) inhibit antibody formation, and (3) prevent rejection of a transplanted kidney with that of both cyclosporin A and tacrolimus. Pimecrolimus administered by means of subcutaneous injection proved to be 8 times and 66 times less potent than cyclosporin A and tacrolimus, respectively, in the graft-versus-host rat model. Subcutaneous tacrolimus was 48 times more

potent than pimecrolimus in inhibiting the development of antibodies to sheep red blood cells. In the transplanted kidney model pimecrolimus was 3 times less potent than cyclosporin A and 15 times less potent than tacrolimus at preventing organ rejection.

In further animal studies, pimecrolimus demonstrated cutaneous local anti-inflammatory properties equivalent or slightly superior to those of cyclosporin A and tacrolimus in models of ACD.⁴⁷ In both mouse and rat models of ACD inhibition, orally administered pimecrolimus was 2 to 4 times more potent than orally administered cyclosporin A and up to 2 times as potent as orally administered tacrolimus. In the mouse, the 2 separate phases of the allergic response, sensitization and elicitation, were evaluated for pimecrolimus, cyclosporin A, and tacrolimus. Primary systemic immune responsiveness, as indicated by antigen sensitization, was not impaired by pimecrolimus, whereas it was inhibited 72% and 60% by tacrolimus and cyclosporin A, respectively. Also, pimecrolimus did not affect lymph nodes, whereas lymph node weight and cellularity were decreased markedly with tacrolimus. In contrast to its lack of effect on sensitization, pimecrolimus inhibited the elicitation phase (ie, the clinical manifestation of ACD) in a dose-dependent manner and to an extent equivalent to tacrolimus. Cyclosporin A was less active.

Given their similar mechanisms of action, a rationale for the above-described differences in the pharmacologic properties of pimecrolimus and tacrolimus has been sought. A possible explanation lies in the higher overall lipophilicity of pimecrolimus compared with tacrolimus (Fig 2). This property may give pimecrolimus a low potential for permeating through the skin and entering the systemic circulation.⁴² Ongoing studies are exploring the validity of this hypothesis. Animal models suggest that the immunomodulatory effect of pimecrolimus might be more selective for skin than those of the immunosuppressants cyclosporin A and tacrolimus. If corroborated in human subjects, its topical anti-inflammatory activity in combination with a low potential for affecting systemic immune function would suggest that pimecrolimus cream has a large therapeutic index for safely and effectively treating cutaneous inflammatory diseases, such as AD.

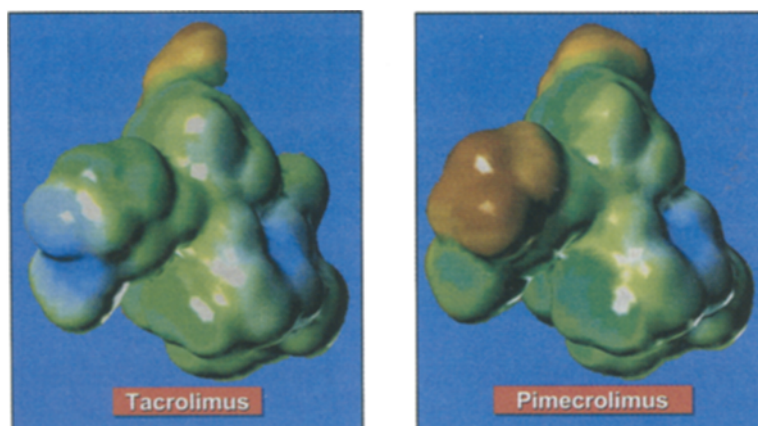


FIG 2. Pimecrolimus is different from tacrolimus: lipophilicity distribution. *Blue* indicates hydrophilic regions; *brown* indicates lipophilic regions.

Elidel's pharmacodynamics and pharmacokinetics

Elidel cream is not a corticosteroid and therefore is not prone to steroid-related adverse effects. Unlike the ultra-potent topical steroid clobetasol-17-propionate, Elidel did not cause skin atrophy in pigs.⁴¹ The lack of atrophogenic potential for Elidel cream was later confirmed in a human study conducted with healthy volunteers.⁴⁸ After 4 weeks of twice-daily treatment, topical corticosteroids (betamethasone-17-valerate 0.1% cream and triamcinolone acetonide 0.1% cream) were associated with significant reductions in skin thickness compared with Elidel or a vehicle control ($P < .001$). Histologic analysis confirmed that significant epidermal thinning was associated with corticosteroid treatment ($P \leq .001$).

In early small-scale clinical trials, Elidel was effective in suppressing signs and symptoms of inflammatory skin disease. It performed as well as clobetasol-17-propionate in plaque-type psoriasis when applied topically under occlusion.⁴⁹ In adults with moderate AD, twice-daily applications of Elidel improved symptom scores without apparent drug-related adverse effects.⁵⁰

Before large-scale clinical trials, the pharmacokinetics of Elidel in patients of various ages with AD was analyzed. In one study the systemic availability of topical Elidel was measured in 22 infants aged 3 to 23 months.⁵¹ Elidel was applied twice daily for 3 weeks to all affected areas, including the face and neck. The percentage of body surface area (BSA) that was affected ranged widely in these infants, from 10% to 92% (Table I), as did values for the area mass ratio (Area mass ratio = Total BSA affected/Body weight), which ranged from 47 to 484 cm²/kg. Pimecrolimus blood concentrations were consistently low, with approximately one third of all samples below the assay limit of quantitation (LOQ; 0.1 ng/mL). A total of 71% were less than 0.5 ng/mL, and fully 98% of the samples were less than 2 ng/mL. Pimecrolimus blood concentrations appeared to correlate with baseline BSA; higher mean concentrations were generally

observed at higher BSAs. However, even among those with the greatest involvement (BSA range, 70%-92%), 26% of pimecrolimus blood determinations were less than the LOQ. By contrast, among those in the lowest range (10% to <40% BSA), 35% of values decreased to less than the LOQ. Pimecrolimus blood concentrations never exceeded 1.8 ng/mL in the group of infants with the most extensive involvement. Because concentrations measured on days 10 and 22 were in a similar range, it appears that pimecrolimus does not accumulate systemically. Pimecrolimus blood concentrations in adults were also found to be low on the basis of a study of 12 patients treated twice daily for 3 weeks with pimecrolimus cream 1%.⁵² In 78% of the 444 blood samples evaluated, pimecrolimus concentrations remained less than the LOQ; the highest concentration measured was 1.4 ng/mL.

A series of long-term pharmacokinetic studies confirmed that repeated application of Elidel does not result in accumulation and appears to have only minimal adverse systemic risk. In 40 adult patients treated for up to 1 year with Elidel, blood concentrations were low, with a maximum blood concentration of 0.8 ng/mL observed in only 2 patients at week 6 of treatment. There was no increase of blood concentration over time in any patient during the 12 months of treatment.⁴³ In 13 adults with hand dermatitis on palmar and dorsal surfaces who were treated with Elidel twice daily for 3 weeks, the maximum blood concentration of pimecrolimus was 0.91 ng/mL. Of a total of 227 samples collected in the course of this study, 74% were less than the LOQ and 98% were less than 0.5 ng/mL. Despite overnight occlusion after the evening application, there was no evidence for systemic accumulation of pimecrolimus between days 8 and 22.⁵³

Comparison with oral pharmacokinetic data

The calculation of standard pharmacokinetic measures for topical Elidel is made difficult by its minimal absorption into the circulation. However, the pharmacokinetics of systemic pimecrolimus have been studied in patients with moderate-to-severe chronic plaque psoriasis who

TABLE 1. Blood concentrations of pimecrolimus in patients with AD, 3 to 23 months of age, treated with Elidel twice daily for 3 weeks (n = 22)

Percentage total BSA range	Area mass ratio* range (cm ² /kg)	No. of samples (no. of patients)	Blood concentration range of Elidel (ng/mL)	Percent of values <0.1 ng/mL†
10-<40	46.5-198.8	40 (9)	<0.1-0.97	35.0
40-<70	194.0-332.5	33 (7)	<0.1-2.26	30.3
70-92	326.8-483.5	27 (6)	<0.1-1.8	25.9

Blood concentrations measured 1 to 3 hours after application on days 1, 10, and 22.

*Total BSA affected/body weight.

†Percentage of blood concentrations measured at less than the assay LOQ of 0.1 ng/mL (LC/MS).

received the drug orally, as well as in healthy subjects. In the psoriasis study, patients received pimecrolimus (5 mg daily to 30 mg twice daily) for 4 weeks. At doses of 20 and 30 mg twice daily, pimecrolimus demonstrated clear clinical efficacy. Blood concentrations of the drug reached steady-state conditions after 5 to 10 days and increased in proportion to the dose. At daily administration of 30 mg twice daily, maximum concentration and 0- to 24-hour area under the curve (AUC_{0-24h}) values at steady state reached 54.5 ng/mL and 589.9 ng·h·mL⁻¹, respectively. Despite the fact that these blood levels were more than 100 times the levels commonly seen in patients receiving topical pimecrolimus, there were no serious adverse events or clinically significant changes in physical examination or laboratory safety test results reported in this study.⁵⁴ The oral data indicate that topical pimecrolimus has a very high margin of systemic safety.

Metabolism, excretion, and toxicity

The metabolism of pimecrolimus has been studied in human subjects by using the radiolabeled drug. After a single oral dose in healthy subjects, unaltered pimecrolimus was the major drug-derived component found in blood. Numerous minor metabolites of moderate polarity, which appeared to be products of *o*-demethylations and oxygenation of the parent compound, were identified.⁴³ Drug-related radioactivity was excreted principally in feces (78.4%), and only a small fraction (2.5%) was recovered in urine. Total mean recovery of radioactivity was 80.9%. The parent compound was not detected in urine, and less than 1% of the radioactivity in feces was accounted for by unchanged pimecrolimus.

Pimecrolimus exhibited a low level of toxicity in animals after administration of excessive doses.⁴³ In a 2-year dermal carcinogenicity study in rats using Elidel, no cutaneous or systemic carcinogenic effects of Elidel were observed up to the highest dose of 10 mg·kg⁻¹·d⁻¹ or 110 mg·m⁻²·d⁻¹ represented by a mean AUC_{0-24h} of 125-ng·h·mL⁻¹ (equivalent to 3.3 times the maximum exposure observed in pediatric patients in clinical trials). In a mouse dermal carcinogenicity study with pimecrolimus in an ethanolic solution, no increase in the incidence of neoplasms was observed in the skin or other organs up to the highest dose of 4 mg·kg⁻¹·d⁻¹ or 12 mg·m⁻²·d⁻¹, corresponding to a mean AUC_{0-24h} value equivalent to 27 times the maximum exposure observed in pediatric patients in clinical trials.

Pimecrolimus does not have intrinsic phototoxicity; the Elidel vehicle did, however, shorten the median time to onset of skin tumor formation in animals.⁴³ The effect of vehicle was observed after chronic topical dosing with concurrent UV ray exposure during 40 weeks of treatment followed by 12 weeks of observation. Pimecrolimus did not contribute to this effect because the time to tumor development did not decrease further with the addition of pimecrolimus to the vehicle cream. In oral and dermal carcinogenicity studies conducted in animals, changes in cellular proliferation were observed only at Elidel doses that far exceeded maximum projected doses in human subjects.⁴³ No drug-related tumors were noted in a mouse oral carcinogenicity study at doses estimated to exceed the maximum recommended human dose by 60- to 133-fold. A carcinogenic effect was not observed until a dose estimated at 258 to 340 times the maximum recommended human dose was administered. Human studies confirm that Elidel has a very low level of toxicity; dermal safety studies have not shown Elidel to induce contact sensitization, phototoxicity, or photoallergy, nor does it exhibit any cumulative irritation.

EFFICACY AND SAFETY OF ELIDEL IN CHILDREN AND ADOLESCENTS WITH AD

Pimecrolimus and Elidel, the 1% cream formulation of pimecrolimus, are products of one of the largest clinical development programs in dermatology. The safety, efficacy, and pharmacokinetics of pimecrolimus have been studied in over 2000 patients with AD, a large proportion of whom were children and infants. The first large-scale trials of Elidel compared its efficacy and safety with that of a corresponding vehicle in pediatric patients with AD 2 to 17 years of age.⁵⁵ Because the studies were of identical design, the pooled results were used for analysis.

A total of 403 patients were randomized to 6 weeks of twice-daily treatment; 267 received Elidel, and 136 received vehicle. The demographic characteristics of the Elidel and vehicle groups were similar. More than 80% of patients in each group were between 1 and 12 years of age, with a mean age for all subjects of 6.7 years. At screening, most of the patients in the study were given a diagnosis of moderate AD. Efficacy parameters included severity of pruritus, Investigator's Global Assessment (IGA) of AD, Eczema Area and Severity Index (EASI) score, and self-assessment of disease control.

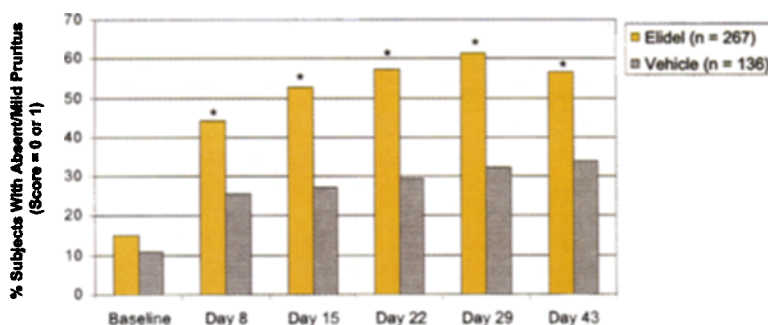


FIG 3. Elidel pediatric study: percentage of subjects with mild or no pruritus. DB, Double-blind; OL, open label. * $P < .001$. Reproduced with permission from Eichenfield et al. *J Am Acad Dermatol*, Vol. 46, Page 500, Figure 4, copyright 2002.

Because pruritus and the itching it evokes are of such great concern in patients with AD, the severity of pruritus was taken as an important subjective measure of clinical efficacy. At baseline, less than 15% of patients in each group reported mild or no pruritus (Fig 3). The effects of Elidel appeared rapidly, with a significantly greater percentage of patients in the Elidel group versus the vehicle group (44.2% vs 25.7%, $P < .001$) reporting mild or no pruritus within the first week of treatment. The proportion of patients in each treatment group reporting relief of pruritus continued to diverge throughout the trial, reaching a peak for the Elidel group at day 29 (61.4%). This level was maintained through day 43, whereas no appreciable change in the proportion of patients reporting pruritus relief was observed in the vehicle-treated group.

The IGA used a 6-point rating scale ranging from 0 to 5 ("clear" to "very severe"). The score measured severity of AD on the basis of morphology at the time of assessment, without reference to the baseline state. An IGA value of 2 or 3 (mild or moderate) was required for inclusion in the trial. A stringent definition of treatment success was used as the efficacy measure: the percentage of patients in each group with an IGA score of 0 or 1 (ie, "clear" or "almost clear" of the signs of AD) at the time of assessment. By the first study evaluation on day 8, 12% of patients receiving Elidel were rated as clear or almost clear compared with 2.2% of patients receiving vehicle ($P \leq .05$, Fig 4). By the final evaluation on day 43, 34.8% and 18.4% of patients receiving Elidel or vehicle, respectively, were similarly rated as clear or almost clear of signs of disease ($P \leq .05$).

Beginning at the first assessment on day 8 and at every subsequent postbaseline assessment, Elidel proved significantly more effective than the vehicle on the basis of mean change from baseline EASI score ($P < .05$). Whereas IGA is a static measure of efficacy that does not refer to a baseline score, the EASI provides a comprehensive efficacy measure that evaluates several anatomic regions for severity, as well as for the extent of key signs of skin inflammation.⁵⁶ Unlike a number of other diagnostic instruments for assessing AD, the EASI emphasizes objective parameters, such as excoriations, erythema, and infil-

tration. As a result, interobserver consistency for the EASI is high. On the basis of EASI scores, eczema on the face and neck responded particularly well to Elidel (Fig 5).

The rate of all adverse events was similar in the Elidel- and vehicle-treated groups. Discontinuations because of adverse events occurred at similarly low rates in the 2 groups, with 1.9% and 2.9% of patients receiving Elidel or vehicle, respectively, dropping out because of such events. The proportion of patients receiving Elidel who reported burning or other local reactions at the site of application was 10.5%, which is similar to the rate of such reactions reported in the vehicle-treated group, which was 12.5%. On the basis of these 6-week studies, Elidel appeared to be both safe and effective when applied twice daily in children with mild-to-moderate AD.

ELIDEL IN INFANTS WITH AD

Because by one estimate 80% of patients with AD are given a diagnosis within the first year of life,⁵⁷ it is important that any treatment for the condition be safe and effective in infants. In a 6-week, double-blind phase of a 26-week study, a total of 186 patients were randomized to twice-daily Elidel ($n = 123$) or vehicle ($n = 63$).⁵⁸ After completion of the double-blind phase, all patients were treated with Elidel in an open-label extension for a further 20 weeks. The demographic characteristics of the Elidel- and vehicle-treated groups were similar. Approximately 50% of the infants were between 3 and 12 months of age, with a mean age for all subjects of 13 months; most had moderate AD at the time of screening.

By using the IGA as an efficacy parameter, rapid and sustained improvement in AD was seen in the Elidel-treated group (Fig 6, left). By the first study evaluation (day 8), 17.0% of patients treated with Elidel were rated as clear or almost clear compared with 9.5% of patients receiving vehicle ($P = .174$). By day 15, the difference in favor of Elidel had risen to the level of statistical significance, with 37.4% and 15.9% in the Elidel- and vehicle-treated groups, respectively ($P < .001$), rated as clear or almost clear. By the end of the double-blind phase on day 43, 54.5% and 23.8% of patients treated with Elidel and vehicle, respectively, were clear or almost clear ($P <$

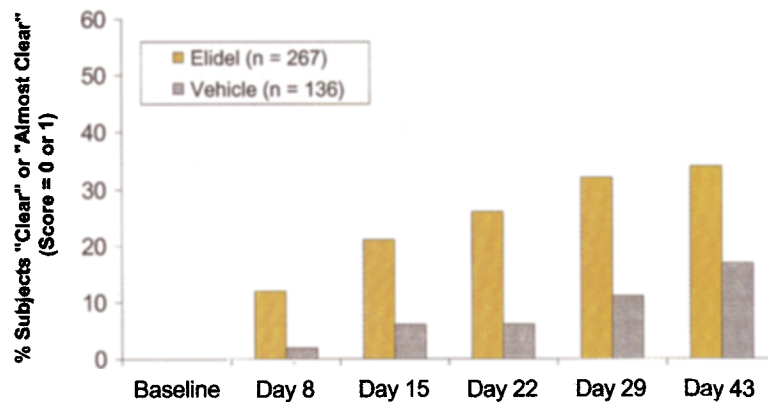


FIG 4. Elidel pediatric study: percentage of subjects "clear" or "almost clear" of AD (IGA score 0 or 1). Reproduced with permission from Eichenfield et al. *J Am Acad Dermatol*, Vol. 46, Page 498, Figure 1, copyright 2002.

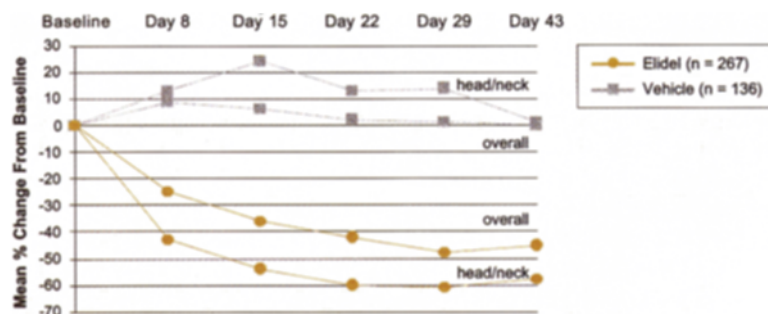


FIG 5. Elidel pediatric study: EASI mean percentage change from baseline (overall, head, and neck). Reproduced with permission from Eichenfield et al. *J Am Acad Dermatol*, Vol. 46, Page 500, Figure 3, copyright 2002.

.001). Efficacy demonstrated in the Elidel-treated group during the double-blind phase was maintained during the 20-week open-label extension, as measured on the basis of IGA (Fig 6, right). Patients who switched from vehicle in the double-blind phase to Elidel during the open-label phase rapidly experienced benefits similar to those seen in patients taking Elidel from the beginning of the study. Beginning at the first assessment on day 8 and at every subsequent postbaseline assessment, Elidel was significantly more effective than vehicle ($P < .001$) on the basis of the other efficacy parameters of pruritus relief, EASI score improvement, and disease-control assessment.

In a shift analysis, a large majority (70%) of subjects with moderate AD who were treated with Elidel had improved symptoms at the 6-week end point; approximately 5% had a worsening of their condition (Fig 7). In contrast, of those with moderate AD who were treated with vehicle, 36% improved and 14% worsened. The majority (65%) of subjects receiving Elidel with mild baseline disease had symptom improvement, and 7.5% had a worsening of their condition by the end of the study. In the vehicle-treated group, 48% of subjects with mild disease at baseline had symptom improvement, and 43% had a worsening of their condition at the end point.

Subgroup analysis indicated that the youngest patients responded well to Elidel. Among infants in the 3-month-old to 1-year-old range, 65.5% achieved clear or almost clear IGA status by day 43, whereas 25% of those in the vehicle-treated group attained a similar level. For infants in the 1- to 2-year-old range, more than twice as many in the Elidel-treated group as in the vehicle-treated group were clear or almost clear at the end of 6 weeks (46.3% vs 22.6%).

The efficacy of Elidel versus vehicle was also demonstrated by the contrast in EASI scores. Clinically and statistically significant ($P < .001$) differences between the 2 groups were recorded as early as the first scheduled assessment on day 8, with the difference continuing to increase during the course of the double-blind phase. Overall median EASI scores decreased by 81.6% from baseline in the Elidel-treated group by the end of the double-blind phase compared with a 25% decrease in the vehicle-treated group. Fig 8 is an example of a treatment success in an infant with moderate baseline AD treated with Elidel for 6 weeks.

Pruritus was rapidly controlled in the Elidel-treated group. At baseline, the majority of patients in both the Elidel- and vehicle-treated groups had moderate-to-

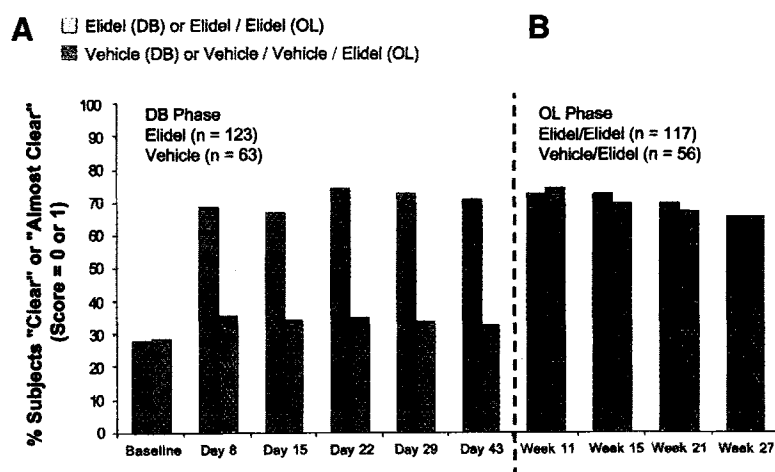


FIG 6. Elidel infant study: patients "clear" or "almost clear" (IGA score of 0 or 1) during double-blind (A) and open-label (B) phases. Note: After completion of the double-blind phase (day 43), patients in the vehicle-treated group were switched to pimecrolimus treatment in the open-label phase. Reproduced with permission from Ho et al. *J Pediatr*, Vol. 142, Page 158, Figure 4, copyright 2003.

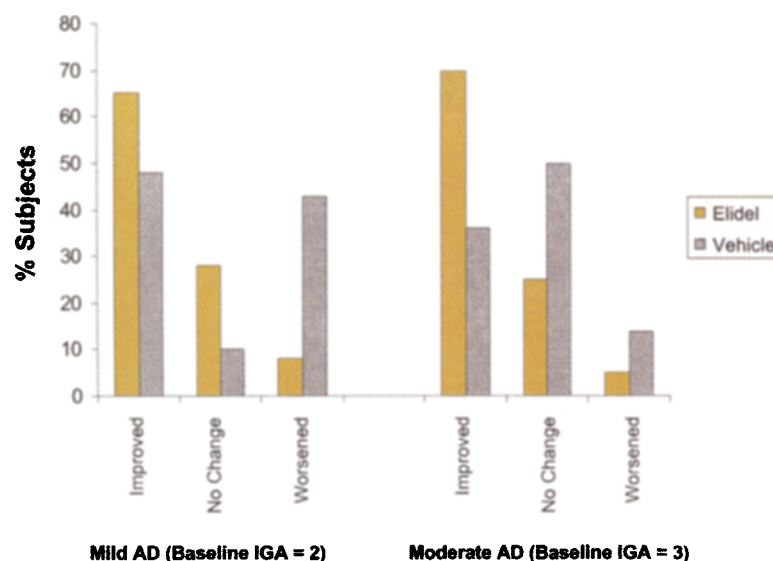


FIG 7. Elidel infant study: shift in IGA score status from baseline to end point (43 days; double-blind phase). Reproduced with permission from Ho et al. *J Pediatr*, Vol. 142, Page 158, copyright 2003.

severe pruritus, but by the first postbaseline assessment on day 8, 69.9% of patients treated with Elidel had no or mild pruritus compared with 36.5% of patients in the vehicle-treated group ($P < .001$). By the end of 6 weeks, pruritus was absent or mild in 72.4% of Elidel-treated patients compared with 33.3% of vehicle-treated patients ($P < .001$). Significant and sustained improvements in pruritus were also observed in vehicle-treated patients once they were switched to open-label Elidel, whereas the effective control of pruritus already established in patients receiving Elidel from the outset was sustained throughout the open-label phase. At week 27, a total of

67.5% of patients treated with Elidel during the double-blind phase and 67.8% of those initially treated with vehicle had either absent or mild pruritus.

Caregiver assessments of disease control in these infants provided a subjective indicator of efficacy. By this standard, infants receiving Elidel demonstrated a substantial improvement in overall disease control relative to those receiving vehicle. At all postbaseline assessments, there were statistically significant differences between the Elidel- and vehicle-treated groups in the distribution of subjects across outcomes, from complete control to uncontrolled disease. At 6 weeks, caregivers



FIG 8. Elidel infant study: an example of an Elidel treatment success. Photos were taken at baseline (A) and day 43 (B). Reproduced with permission from Ho et al. *J Pediatr*, Vol. 142, Page 157, Figure 3, copyright 2003.

assessed that there was complete or good control in 71.5% of patients compared with 27.0% of patients in the vehicle-treated group ($P < .001$).

Elidel was safe and well tolerated, both in the double-blind phase and throughout the open-label extension. No patients discontinued the study in the double-blind phase because of adverse events. During the double-blind phase, 74.8% of patients in the Elidel-treated group and 65.1% in the vehicle-treated group experienced at least 1 adverse event, most of which were unrelated to study medication. These were mild to moderate in severity and reflected typical childhood illnesses (eg, gastroenteritis, teething pain, cough, and otitis media). Adverse events

reported as related to study medication for the Elidel- and vehicle-treated groups occurred at rates of 5.7% and 12.7%, respectively.

The local tolerability of Elidel during the 6-week double-blind phase was excellent, with application-site events, such as irritation, burning, and erythema, occurring at rates of less than 2%. The incidence of other local adverse events was similar between the 2 treatment groups, although bacterial infection rates in vehicle-treated subjects were higher. Contact dermatitis, which for the purposes of the study included diaper rash, was usually mild to moderate in severity and not considered related to study medication. There were no clinically significant dif-

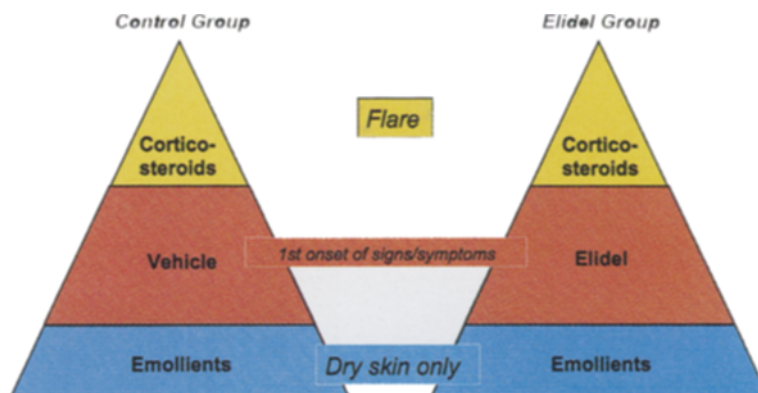


FIG 9. Design of long-term study comparing early intervention with Elidel with a conventional AD treatment strategy.

ferences between the treatment groups with respect to the incidence of bacterial or viral skin infections.

During the open-label phase, adverse events were reported in approximately 80% of subjects and in similar proportions, regardless of previous double-blind treatment. Three (2.6%) drug-related adverse events were recorded for patients taking Elidel during the double-blind phase compared with 5 (8.9%) in the double-blind vehicle-treated group. Skin infections were reported in approximately 17.9% of the subjects ($\geq 2\%$), regardless of treatment during the previous phase.

In summary, the efficacy and safety of Elidel in infants has been demonstrated, with rapid and sustained clinical benefits observed for infants with mild-to-moderate AD. Elidel appears to possess a high benefit/risk ratio in infants and has the potential to be a valuable adjunct to the limited treatment options currently available for the treatment of AD in young children.

ELIDEL IN THE LONG-TERM MANAGEMENT OF PEDIATRIC AD

Because AD is a chronic or chronically relapsing condition that primarily affects children, treatment of vulnerable age groups for extended periods is frequently required. Therefore, in addition to being effective, any medication used for the condition must be particularly well tolerated and safe. A 1-year study of pediatric patients (2-17 years of age) with AD ranging from mild to severe was undertaken to establish the long-term safety and efficacy of Elidel.⁵⁹ A further goal was to determine whether early treatment of the signs and symptoms of AD with Elidel could influence long-term outcomes by preventing disease flares.

The study compared Elidel treatment with a conventional AD treatment strategy of emollients and topical corticosteroids. A total of 713 patients were randomized 2:1 to an Elidel-based or control regimen. Both groups used emollients for dry skin, but at the appearance of early AD signs or symptoms (eg, itching and persistent redness), one group used Elidel to prevent progression to flares, and the

control group used vehicle. If flares occurred, moderate-potency topical corticosteroids were to be used by patients in both groups. The study design is schematically depicted in Fig 9. In effect, Elidel was used as a first-line therapy to prevent progression of active disease, with topical steroids reserved as second-line therapy to treat any Elidel breakthrough flaring. The primary efficacy end point was the number of flares over the first 6 months. Secondary end points included the number of flares over the entire 12 months of the study and the time to a first flare. The number of days of corticosteroid use was recorded for both treatment groups to determine whether Elidel treatment might have a steroid-sparing effect.

Over the first 6 months, Elidel significantly reduced both the incidence of flares and the use of second-line topical corticosteroids. In the Elidel-treated group 61.0% of patients completed 6 months without a flare compared with 34.2% of patients in the control group ($P < .001$, Fig 10). At 12 months, 50.8% and 28.3% of patients in the Elidel-treated and control groups, respectively, were flare free ($P < .001$). A subgroup analysis found that after 6 months, Elidel significantly decreased the number of flares across all baseline severities (Fig 11), including among patients initially classified as having severe AD.

Patients receiving Elidel required less topical corticosteroid therapy than control patients. After 6 months, 35.0% of those in the Elidel-treated group and 62.9% of those in the conventional therapy control group received corticosteroids. A decreased need for steroids was maintained throughout the study, with 42.6% and 68.4% of those in the Elidel-treated and control groups, respectively, receiving steroid treatment by month 12. Among those who required topical corticosteroids, the duration of such therapy over a 6-month period was shorter in the Elidel-treated group, with 17.1% and 27.5% of patients in the Elidel-treated and control groups, respectively, receiving 1 to 14 days of therapy and 25.5% and 41.0%, respectively, receiving steroids for longer than 14 days.

It is noteworthy that the steroid-sparing effect of Elidel was apparent, even though the Elidel-treated patients were in the study longer than patients in the control

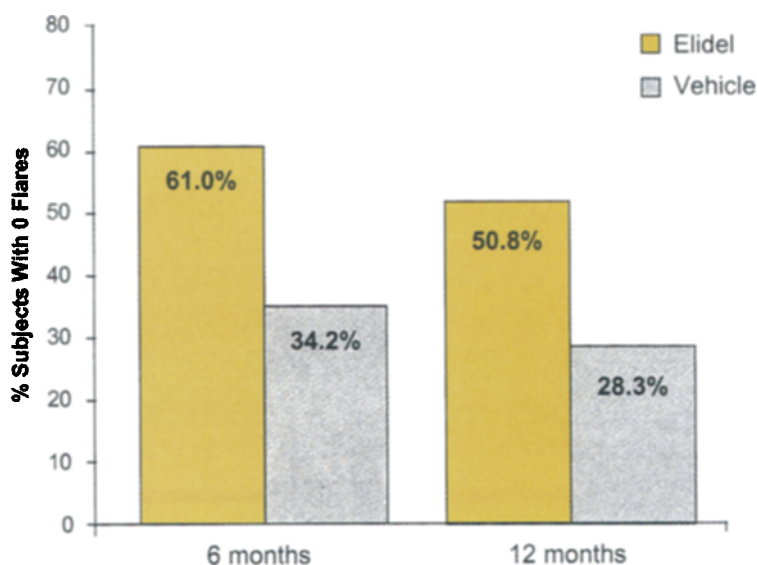


FIG 10. Long-term management of pediatric AD with Elidel: patients with 0 flares at 6 and 12 months. Reproduced with permission from Wahn et al. *Pediatrics*, Vol. 110, Page e29, copyright 2002.

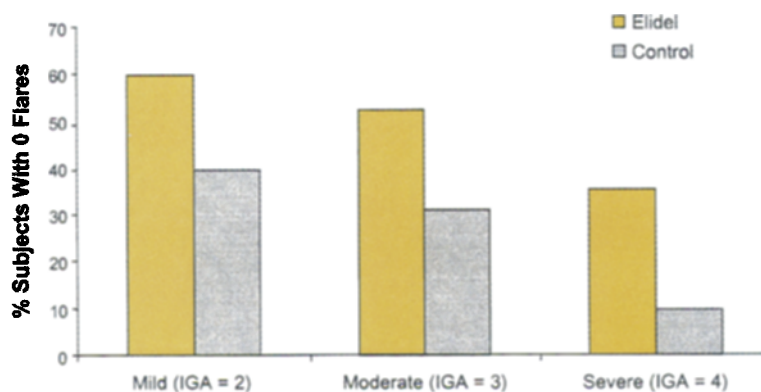


FIG 11. Long-term management of pediatric AD: proportion of patients with 0 flares after 6 months by disease severity at baseline. Reproduced with permission from Wahn et al. *Pediatrics*, Vol. 110, Page e29, Figure 2B, copyright 2002.

group, as indicated by a lower rate of premature discontinuation in the Elidel-treated group. The discontinuation rate was significantly higher among control patients than among Elidel-treated patients (51.5% vs 31.6% at 12 months), and proportionately more patients with severe or very severe disease discontinued in the control group. The main reason for the higher discontinuation rate in the conventional-therapy group was unsatisfactory therapeutic effect (30.4% vs 12.4%). Other reasons for discontinuation (eg, adverse events, abnormal laboratory values, and protocol violation) occurred at similar rates in the 2 treatment groups.⁶⁰

Lower rates of corticosteroid use and discontinuation in the Elidel-treated group are consistent with the observation that, for the 12 months of the study, the time to a first flare was significantly longer in the Elidel-treated group than in the control group ($P < .001$, Fig 12). The

decreased incidence of AD flares in the Elidel-treated group, with consequently less need for corticosteroids to treat flares, is consistent with the observed changes in EASI scores (Fig 13). Over time, median EASI scores in the Elidel-treated group were substantially lower, thus indicating better disease control than in the control group.

On the basis of analyses at the 6- and 12-month end points, Elidel was well tolerated. There was no significant difference between treatment groups in the 12-month rate of application-site burning, which occurred in 10.5% and 9.3% of Elidel-treated and control patients, respectively ($P = .484$). There were no important differences between treatment groups in the duration or severity of application-site reactions. Most such reactions were mild to moderate and transient, occurring within the first week of treatment. Other adverse events were mostly common childhood ailments and infections, the rates

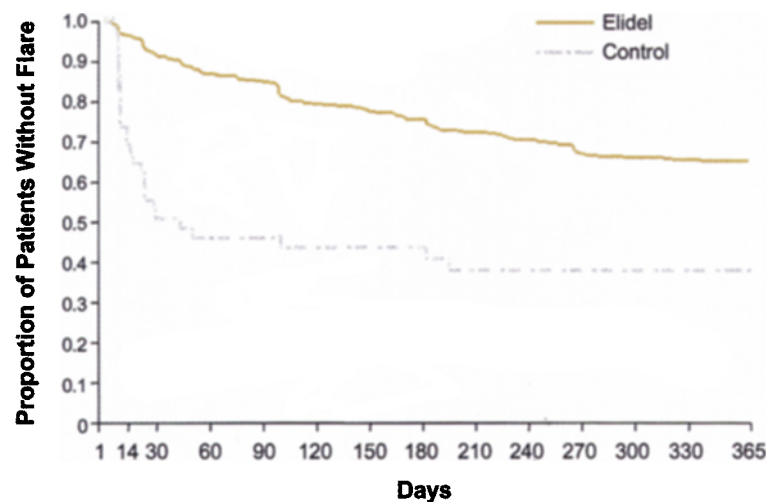


FIG 12. Long-term management of pediatric AD: Kaplan-Meier estimate of time to first flare. Reproduced with permission from Wahn et al. *Pediatrics*, Vol. 110, Page e29, Figure 2A, copyright 2002.

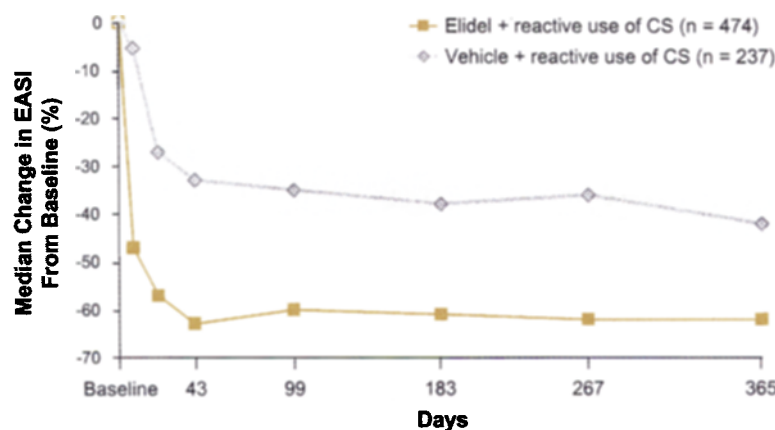


FIG 13. Long-term management of pediatric AD: median percentage reduction in EASI score over 12 months (Elidel vs conventional therapy). CS, Moderately potent corticosteroid. Reproduced with permission from Wahn et al. *Pediatrics*, Vol. 110, Page e29, Figure 2B, copyright 2002.

of which were not significantly different between groups. Incidence rates of the most common adverse events observed in the study are listed in Table II. The rates were adjusted to account for the fact that the Elidel-treated group had a longer mean follow-up period because fewer patients discontinued from that group compared with the control group. The mean duration of follow-up was 303.7 days in the Elidel-treated group and 235.2 days in the control group.

With regard to skin infections, there were no significant differences between groups in the time to first occurrence of bacterial skin infections or in the time-adjusted incidence of bacterial skin infections. The incidence of grouped viral skin infection was somewhat higher in the Elidel-treated group than in the control group (12.4% vs 6.3%, $P = .038$), although a significant difference in infection rate was not seen for any single specific viral infection. Although it might not be clinically significant, there

was a greater incidence of cough in the Elidel patients in this study. A recall antigen test was administered to patients who completed 12 months of study to determine whether long-term Elidel treatment impaired skin immune responses. Tetanus, diphtheria, streptococcus, tuberculin, and *Candida* species skin were among the antigens tested. Overall, there were no significant differences between the 2 treatment groups in response to recall antigens among patients completing 12 months of the study.⁵⁹

On the basis of the results of this study, patients with AD can safely derive substantial clinical benefit through long-term Elidel treatment. The treatment paradigm used in this study represented a shift from conventional AD treatment strategies, in which emollients are applied for skin care and reactive use is made of corticosteroids to treat disease flares. Instead, by treating early AD signs or symptoms with Elidel, flaring was significantly reduced. This was associated with a decreased need for topical

TABLE II. Adjusted incidence of most common adverse events ($\geq 10\%$): Elidel versus conventional therapy

Adverse event	Elidel, % (n = 474)	Control, % (n = 237)	P value*
Nasopharyngitis	28.9	27.1	.944
Headache	23.0	21.5	.576
Bronchitis	13.2	13.7	.794
Influenza	14.6	9.5	.083
Cough	19.3	11.8	.045
Pyrexia	15.4	11.8	.326
Application-site burning	10.5	9.3	.484

*P value from time-to-first-occurrence analysis (log-rank test). Reproduced with permission from Wahn et al. *Pediatrics*, Vol. 110, Page e29, Table 3, copyright 2002.

corticosteroids. In fact, more than half of the patients were able to eliminate corticosteroids altogether. Better long-term control of AD, assessed by means of EASI, was evident as well. The rates of local and systemic adverse effects in the Elidel-treated group were comparable with those in the control group, with little effect by Elidel on systemic immunity.

ELIDEL IN THE LONG-TERM MANAGEMENT OF AD IN INFANTS

A long-term study conducted in infants aimed to determine whether pimecrolimus cream could reduce the incidence of flares in very young patients when applied at the early signs and symptoms of acute AD.⁶⁰ The study was similar in design to the long-term study conducted in children. A total of 251 infants aged 3 to 23 months with AD (IGA score ≥ 2) were randomized 4:1 to a pimecrolimus-based regimen (n = 204) or a conventional treatment regimen (n = 47). As in the children's study, both groups used emollients for dry skin. Early AD signs and symptoms (itching, redness, or thickening) were treated either with pimecrolimus cream 1% to prevent progression to a flare or, in the control group, with vehicle. In the event of flares (IGA score of 4 or 5), moderately potent corticosteroid use was permitted in both groups.

Pimecrolimus significantly reduced the incidence of flares compared with control treatment ($P < .001$), with 67.6% and 30.4% of patients, respectively, completing 6 months without a flare. After 12 months, 56.9% of infants in the pimecrolimus group and 28.3% in the control group experienced zero flares. An analysis of time to first flare found that treatment with pimecrolimus was associated with a significantly longer flare-free period ($P < .001$). In addition, the mean number of flares per unit of time was significantly lower in the pimecrolimus group than in the control group (1.0 vs 2.2 per 12-month period, $P < .001$).

Consistent with the reduction in the incidence of flares, overall corticosteroid use was substantially lower in the pimecrolimus-treated group than in the control group: 63.7% versus 34.8% of patients did not use corticosteroids at all during the study. Skin quality, as judged by IGA score, was better in the pimecrolimus-treated group than in the control group. More patients receiving pimecrolimus achieved clear or almost clear skin (IGA

score of 0 or 1). By day 8 (the first postbaseline visit), an IGA score of 0 or 1 had been achieved in 44.6% of pimecrolimus-treated patients compared with only 8.7% of patients receiving control treatment ($P < .001$). The maximum benefit was achieved by approximately day 22 in the pimecrolimus-treated group compared with month 3 in the control group, and the magnitude of the effect was greater in the pimecrolimus-treated group (54.9% vs 39.1% achieving an IGA of 0 or 1 by day 22, $P = .034$). Pimecrolimus was also more effective in controlling pruritus on the basis of caregiver assessment. A significantly greater proportion of subjects in the pimecrolimus-treated group than in the control group had no pruritus or mild pruritus after 6 months (73.0% vs 54.4%, $P = .008$).

Both treatments were well tolerated, and with the exception of viral infection (not otherwise specified as to type), which was more common in the control group, there were no clinically significant differences between the treatment groups with respect to incidence of common adverse events. An important observation in such young patients was the fact that the incidence of application-site reactions was low in both groups (6.5% vs 14.7% pimecrolimus vs control); there were no significant differences between the treatment groups ($P = .104$).

In conclusion, this study demonstrated that early intervention with pimecrolimus to prevent progression to disease flare was significantly more effective than conventional management for modifying the long-term course of AD in infants. Infants receiving pimecrolimus had fewer flares and less need for corticosteroids. This study complements the results of the short-term infant study, demonstrating the efficacy and safety of pimecrolimus for AD in infants, a group for which there are currently a limited number of treatment options.

CONCLUSION

Elidel is distinct from other currently available topical nonsteroidal AD medications because it was specifically developed to treat inflammatory skin diseases. Elidel targets immunologic pathways important for the development of AD, without apparent effects on systemic immunity and without causing dermal thinning. The efficacy and safety of Elidel have been demonstrated in patients with mild-to-moderate AD. As early as the first week of treatment, patients treated with Elidel showed significant

improvement in the signs and symptoms of AD, including pruritus, the most troublesome of AD symptoms. The overall incidence of adverse events, including bacterial and viral infections, was comparable between Elidel- and vehicle-treated patients. In a 1-year long-term study in which Elidel was used at the first signs of eczema, patients using Elidel had fewer flares and less need for topical corticosteroids to control severe flares. Elidel cream 1% has the potential to provide clinicians with a safe and effective nonsteroidal alternative for the short-term treatment and long-term management of AD.

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