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Pimecrolimus 1% Cream for the Treatment of Atopic Dermatitis

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ABSTRACT

Atopic dermatitis is a highly pruritic inflammatory disorder of the skin characterized by onset in infancy or childhood and a chronically relapsing course. Mainstay treatments are emollients and topical corticosteroids, but the latter are limited by side-effects from long-term use. Pimecrolimus is an ascomycin macrolactam derivative and a calcineurin inhibitor that targets T-cell activation but does not inhibit antigen-presenting cells in the skin. In multiple clinical trials comprising more than 19,000 patients, pimecrolimus cream has been shown to be very effective in suppressing atopic dermatitis and to have an excellent safety profile. This has also been shown in long-term studies (>2 years) and by postmarketing experience.

Key Words: *atopic dermatitis, calcineurin inhibitor, pimecrolimus*

Atopic Dermatitis (AD)

AD is a highly pruritic inflammatory disorder that is characterized by childhood onset and that usually assumes a chronically relapsing course.[1] The incidence of AD has increased in recent years with a prevalence of 7%-21% in school-age children, but it is also common in adolescents and adults.[1] Immunologic abnormalities play a fundamental role in the development of the disease, but environmental factors such as *Staphylococcus aureus*, dust-mites, or pollens contribute to the onset and exacerbation of AD. In response to antigens, levels of circulating IgE antibodies increase, giving rise to excessive T-cell activation. This in turn leads to an overproduction of cytokines, thus initiating and sustaining dermal inflammation.[1] Levels of natural defense proteins such as cathelicidins and defensins are significantly decreased in the skin of AD patients. The essential features of AD are dry skin, pruritus, and eczema with an acute, subacute, or chronic relapsing course. The mainstay of the treatment of AD is the use of emollients, as well as topical corticosteroids. In more severe cases, phototherapy, photochemotherapy, and the use of immunosuppressants is used.[1] Although undoubtedly effective, corticosteroids have been limited by side-effects, such as skin atrophy and even systemic effects, including hypothalamic-pituitary-adrenal axis suppression and growth inhibition. In the past, therefore, the therapeutic armamentarium available for AD clearly indicated the need for the development of anti-inflammatory compounds that are both effective and not limited by side-effects, making them suitable for prolonged use in a chronic skin disease that greatly reduces the quality of life.

Pimecrolimus

Pimecrolimus, an ascomycin macrolactam derivative, is a calcineurin inhibitor that binds with high affinity to the cytosolic receptor macrophilin-12, inhibiting the calcium-dependent phosphatase calcineurin, an enzyme required for the

dephosphorylation of the cytosolic form of the nuclear factor of the activated T cell (NF-AT).[2] It thus targets T-cell activation and proliferation by blocking the release of both TH1 and TH2 cytokines such as IF-g, IL-2, -4, -5, and -10.[3] It also prevents the production of TNF-a and the release of proinflammatory mediators such as histamine, hexosaminidase, and tryptase from activated mast cells.[3] It does not have general antiproliferative activity on keratinocytes, endothelial cells, and fibroblasts, and in contrast to corticosteroids, it does not affect the differentiation, maturation, functions, and viability of human dendritic cells.[4] As shown in mice, topical pimecrolimus does not affect epidermal Langerhans cells or antigen-presenting cells that play a key role in the local immunosurveillance.[5] A recent study confirmed that for the treatment of AD, betamethasone, but not pimecrolimus, results in the depletion of Langerhans cells. Both drugs significantly reduce T cells in skin biopsies, demonstrating a more selective mode of action of pimecrolimus vs. corticosteroids.[6]

In animal models of skin inflammation pimecrolimus is highly active after both topical and systemic application and its effects differ considerably from those of corticosteroids, cyclosporin and tacrolimus.[7] Although pimecrolimus combines high anti-inflammatory activity in the skin, it has a low potential to impair systemic immune reactions, and topical application in humans is not associated with the atrophogenic side-effects observed with corticosteroids.[7] Pimecrolimus blood levels remain consistently low after repeated topical application and no clinically relevant drug-related systemic adverse events have been reported among the patients treated in clinical trials so far.[7] Pimecrolimus is approved as a 1% cream (Elidel™, Novartis) in 83 countries and has been given approval by both the US FDA and Health Canada for the short-term (acute) and long-term intermittent treatment of AD.

Clinical Trials

The efficacy of topical pimecrolimus has been established in clinical studies in adults, children, and infants in both short-term treatment and long-term management.[7] In an initial double-blind, right and left arm comparison proof of concept study in adults with AD, pimecrolimus proved to be more effective than the vehicle. Patients receiving pimecrolimus twice daily achieved a mean Atopic Dermatitis Severity Index (ADSI) reduction at the endpoint of 71.9% compared with 10.3% in the vehicle group. A significant therapeutic effect was already being observed by day 2.

In a multicenter dose finding study comparing the efficacy of 0.05%-1% pimecrolimus in adults with mild-to-severe AD, a clear dose-effect relationship was seen.[8] Two hundred sixty patients were randomized to receive pimecrolimus at concentrations of 0.05%, 0.2%, 0.6%, or 1%, a vehicle, or 0.1% betametasone 17-valerate cream b.i.d. for up to 3 weeks. Using the Eczema Area and Severity Index (EASI), no therapeutic effect was observed with 0.05% pimecrolimus, but all other concentrations of pimecrolimus cream proved to be significantly superior to the vehicle.[9] Efficacy was clearly dose-dependent with 1.0% pimecrolimus cream showing the greatest efficacy and a 47% median reduction of EASI from baseline. A significant reduction of the pruritus score from baseline was demonstrated for 1% pimecrolimus cream over the other concentrations and this was subsequently selected for further studies.

Short-term efficacy of pimecrolimus in acute flares of AD was studied in children and adolescents (aged 1-17 years), and in infants (aged 3-23 months).[9,10] A design was used whereby the initial double-blind, vehicle-controlled phase patients were randomized 2:1 to be treated with pimecrolimus or vehicle twice daily for 6 weeks. This was then followed by a 20-week open-label phase where all patients received pimecrolimus twice daily. Treatment success was assessed by the Investigators' Global Assessment (IGA) and EASI scores.

Two studies in children and adolescents were pooled and a total of 403 patients (1-17 years of age), with a baseline IGA score of 2 or 3 and AD affecting at least 5% of the total body surface area, were randomized to receive pimecrolimus (n=267) or vehicle (n=136). The results revealed a significantly higher efficacy for pimecrolimus than vehicle. Significantly more pimecrolimus-treated patients had an IGA of 0 or 1 on day 8 compared with the vehicle-treated patients ($p<0.01$), and thereafter, the proportion of pimecrolimus-treated patients who experienced treatment success increased continuously over time until the end of the double-blind phase.[7] This was also reflected by the assessment of the EASI score. Pimecrolimus was particularly effective in the head and neck area, and a significant relief from pruritus was observed within the first week of pimecrolimus treatment ($p<0.001$).

In the subsequent 20-week, open-label phase, the therapeutic effect was maintained in the pimecrolimus group and a rapid overall improvement was noted in the patients previously treated with the vehicle alone. Using the Parents' Index of Quality of Life in Atopic Dermatitis (PIQoL-AD), a significant improvement was found in patients younger than 8 years of age. An identical study performed in infants (3-23 months) showed similar results.[7] In a total of 186 patients with an IGA score of 2 or 3, 89% of patients in the pimecrolimus group completed the study compared with 52% in the vehicle group, and at the end of the 6-week double-blind phase, 54.5% of the pimecrolimus-treated patients were almost clear compared with 23.8% in the vehicle group

(p<0.001). After 6 weeks of treatment, a greater than 80% median reduction of EASI was observed and was maintained during the following 20-week open-label period. Again, change from vehicle to pimecrolimus in the open-label extension resulted in a rapid and profound improvement of EASI in the patients previously treated with vehicle alone.

Long-Term Treatment

Three multicenter, double-blind controlled studies in infants, children, and adults compared the efficacy and safety of pimecrolimus with conventional treatment based on the reactive use of corticosteroids.[7] Patients were randomized to receive either pimecrolimus or control treatment, and in both groups emollients were used for general skin care throughout the studies. At the first appearance of signs or symptoms of AD, patients received either pimecrolimus or vehicle twice daily until complete remission was achieved. When the disease was not adequately controlled by this treatment, a moderately potent topical corticosteroid was provided as "rescue" medication after which the study medication was resumed. Endpoints measured were the number of flares requiring topical corticosteroids within a period of 6 months (in all studies) and within 12 months in the infant- and children-only studies. In infants treated with pimecrolimus, 68% remained without a single corticosteroid-requiring flare for 6 months, compared with 30% of patients in the control group. In all three studies the percentage of patients completing 6 months without flare was significantly higher in the pimecrolimus group than in the controls (p<0.001). About twice as many patients remained flare-free in the pimecrolimus group after 1 year of treatment compared with the group receiving conventional therapy.[6] Superior control of AD by the treatment employing pimecrolimus was particularly obvious when the number of days requiring corticosteroid treatment was compared with conventional treatment. The proportion of patients requiring corticosteroids was significantly reduced in all age groups (Table 1).

In the adult study, the severity of pruritus decreased significantly in the pimecrolimus group compared with the control group as early as 48 hours after beginning treatment (p<0.001).[7]

Population	Pimecrolimus Group	Control Group
Infants (<2 years)	70	39
Children (2-17 years)	66	38
Adults (>18 years)	49	22

Table 1: Proportion of patients not requiring topical corticosteroids

In conclusion, pimecrolimus has proven highly effective in reducing the signs and symptoms of AD in long-term clinical trials, and this has been observed in infants, children, and adults. Significant improvement can be seen after the first few days of treatment and in long-term studies pimecrolimus demonstrated the ability to prevent disease progression and to reduce flares as measured by a reduction of the necessity of employing "rescue" corticosteroid treatment.

In clinical practice more than 5 million patients have been treated since December 2001. Of these, roughly 2.7 million patients were younger than 10 years of age. The average pimecrolimus usage was 1.6g/day used intermittently, 45 days/year.[11]

Pharmacokinetics

Pimecrolimus levels in the blood were measured after treatment with 1% pimecrolimus cream twice daily for up to 1 year in adults, infants and children.[7] A review published in 2004 identified several open-label, noncontrolled, pharmacokinetic studies of adult patients with moderate-to-severe AD who were treated with pimecrolimus cream on all affected areas for 3 weeks, and had blood concentrations below the level of detection (level of quantitation [LoQ]=0.5ng/ml) in 78% of 444 samples evaluated; the highest concentration observed was 1.4ng/ml.[7]

In another study where 44 patients with moderate-to-severe AD were treated for up to 1 year, 13 patients completed 1 year in the study. A total of 98% of the 918 concentrations measured remained below the LoQ of 0.5ng/ml and the highest concentration observed was 0.8ng/ml without drug accumulation.[7]

Children and infants

- aged 1-4 years with an affected body surface area (BSA) of 23%-69%
- aged 4 months-14 years old with a BSA of 21%-80%
- aged <23 months with a BSA of 10%- 92%,

who were all treated with pimecrolimus, showed blood concentrations of pimecrolimus below 2ng/ml in 99% of readings. Only 10 out of 75 patients had measurable AUCs, ranging from 11-39ng*h/ml. Even in patients with large affected areas (70%-92%), the blood concentrations were between <0.1-1.8ng/ml and were thus consistently low. No drug accumulation was observed in any of the patients, including patients treated with pimecrolimus for up to 1 year. These data show that topical treatment of AD with pimecrolimus leads to a minimal systemic exposure irrespective of the extent of the body area treated. It should also be noted that the single highest

AUC ever measured (38ng*h/ml) is approx. 14 times less than the minimal AUC needed to treat psoriasis with the oral formulation of pimecrolimus and 27 times less than the NOAEL (No Observed Adverse Effect Level) in rodents, suggesting a comfortable safety profile.[12]

Tolerability and Safety

There is a large safety database available for topical pimecrolimus from more than 19,000 patients treated in clinical studies since 1996. This includes ~3,000 infants (3-23 months) and more than 7,000 children aged 2-17 years who have been treated with topical pimecrolimus in clinical trials for up to 2 years.[11]

Systemic Side-Effects

No clinically relevant systemic side-effects have been noted in AD patients treated with pimecrolimus cream in clinical trials to date.[7] This is in line with the observation that treatment of AD patients with pimecrolimus leads to minimal or negligible systemic exposure even in patients with large body surface areas affected as discussed above. A study involving 251 infants randomized to topical pimecrolimus or vehicle for 1 year showed no significant difference between groups in the incidence of adverse effects.[7] More importantly, in a recently published study comparing the adverse event profile in infants after 1 and 2 years of pimecrolimus long-term management, the overall incidence of adverse events decreased over time,[13] suggesting no impact on the developing immune system in infants.

Application-site Reactions

The most frequently reported application-site reaction is a sensation described as burning or a feeling of warmth, which has occurred in about 15% of adults and in 7% of pediatric patients. These sensations are transient and usually resolve after a few days of treatment. Other application-site reactions are irritation, erythema, and pruritus, which were generally observed early in treatment and were mild and of short duration. There was no significant difference between the pimecrolimus and control groups.[7]

Skin Infections

Topical treatment with 1% pimecrolimus cream is not associated with an increase in skin infections as compared with corticosteroids or vehicle. The incidence of fungal and viral infections was not increased significantly with pimecrolimus. In the clinical pivotal program, only one case of virologically proven eczema herpeticum was observed in a patient on pimecrolimus. The incidence of clinically diagnosed eczema herpeticum (i.e., nonvirologically proven) was 0.5 in 1,000 control-treated subjects compared with 1 in 1,000 pimecrolimus-treated patients, but the difference was not significant. Postregistration studies do, however, show an increased, albeit small, risk of viral skin infections, mostly herpes simplex, in pimecrolimus-treated children as compared with vehicle-treated patients. The relative risk for all viral skin infections vs. vehicle is 1.6 and for herpes simplex specifically, 2.2. Of note, in a 1-year, randomized controlled trial of pimecrolimus vs. topical corticosteroids (n=658), the incidence of herpes simplex was similar in both groups (topical corticosteroids: 5.5%, pimecrolimus 6%).[14]

Systemic Infections

No overall differences in the incidence of systemic infections between pimecrolimus cream-treated and control groups was observed in all analyses. The few imbalances were equally distributed between the pimecrolimus and the vehicle groups.[12]

Phototoxicity and Photocarcinogenicity

According to the European Summary of Product Characteristics, pimecrolimus has shown no phototoxicity or photocarcinogenicity in standard animal models.

Delayed-Type Hypersensitivity

The response of skin to recall antigens was tested after 1 year of treatment with pimecrolimus or conventional treatment in order to evaluate the effect of pimecrolimus on delayed-type hypersensitivity. No significant differences were observed between the two treatment groups using a range of common bacterial and fungal antigens. This seems to indicate that topical pimecrolimus does not impair the skin immunosurveillance of the patient.[7]

Vaccination Response

Topical pimecrolimus treatment has no effect on the vaccination response in infants and children. Protective antibody titer levels to rubella, measles, diphtheria, and tetanus in pimecrolimus-treated pediatric patients were not different from the range in the general population.[15]

Malignancies

Clinical studies show no evidence of increased risk of malignancies in patients treated with pimecrolimus. As of January 2005, seven cases of malignancies were reported in clinical trials, two of which occurred among the ~19,000 patients using pimecrolimus and five of which occurred within the ~4,000 control patients. The malignancies occurring in the pimecrolimus-treated patients were one squamous cell carcinoma (65-year-old female) and one case of colon cancer (male, 47-years) whereas the malignancies occurring in the control groups were one each of gastric carcinoma (male,

67-years), melanoma (male, 64 years), histiocytosis X (male, 5 years), leukemia (female, 5 months), and one thyroid cancer (female, 65 years). Continuous reporting on malignancies outside clinical trials up to March 2005 showed 17 patients with malignancies. These were five patients with skin tumors (one basal cell carcinoma, two squamous cell carcinomas, and two "skin carcinomas"), 10 patients with lymphoma (three <3 years, two aged 40-49, and five aged >50), one myelodysplastic syndrome, and one breast cancer. Stratifying these cases according to age, type of cancer, and the incidence of spontaneous occurrence of these cancers in the normal population shows that the incidence of the reported malignancies is far below the expected number of cases in the general population. No causality between pimecrolimus use and the occurrence of malignancy can be established. This issue has also been evaluated by an independent expert committee, which found no causality between spontaneous reports of lymphoma and pimecrolimus.[16]

Summary on Safety

There is no clinical evidence for increased risk of malignancies after the use of pimecrolimus cream, and there is no evidence for systemic immunosuppression by topical pimecrolimus. These facts become particularly evident when considering the immunocompetence and infection rates in children having received pimecrolimus. These outcomes are also improbable on the basis of pharmacokinetic considerations.

Black Box Warning Label

Earlier this year, the US FDA announced that it was considering adding a black box warning label on pimecrolimus (and also on tacrolimus) based on a recommendation of its Pediatric Advisory Committee because of a potential risk of cancer. At the time of writing no black box warning had been issued. This concern of the FDA is based on the postmarketing spontaneous reports on cancers discussed above, the theoretical concerns of carcinogenicity by immunosuppression, and a cynomolgus monkey study with an oral formulation of pimecrolimus which demonstrated an occurrence of transient lymphomas in the lowest dose, which was >30 times higher than the highest AUC in humans after application of the cream formulation. The American Academy of Dermatology expressed disappointment about this action, "despite the fact that there is no data that proves that proper topical use of pimecrolimus (and tacrolimus) is dangerous in people."[17] Similarly, the ISDI (Inflammatory Skin Disease Institute) has expressed disappointment with the decision and presented testimonies regarding this issue.[18] The topical Calcineurin Inhibitor Task Force of the ACAAI and AAAI[19] have stated that "none of the information provided for the cases of lymphoma associated with the use of topical pimecrolimus (or tacrolimus) in AD indicate or suggest a causal relationship" and concluded "that there was no clear-cut link between pimecrolimus (or tacrolimus) and increased risk of lymphoma"; also, they state that "there is no evidence of systemic immune suppression from topical pimecrolimus (or tacrolimus) as measured by response to childhood immunization and delayed hypersensitivity." Further, they say that "the topical Calcineurin Inhibitor Task Force of ACAAI and AAAI concludes that based on current data the risk-benefit ratio of topical pimecrolimus (and tacrolimus) are similar to most conventional therapies for the treatment of chronic relapsing eczema." A number of organizations in the US and in Europe share this view, and the general question is why the FDA decided to take this step despite the fact that current data provide no basis for suggesting an increase in the risk of neoplasia. In the opinion of many experts with whom I have spoken, there is no unequivocal answer to this question. It is an opinion that I share. It seems that the FDA has decided to exercise particular caution in the use of topical calcineurin inhibitors outside the approved indications and therefore wants to limit the practice of off-label use. Many believe, and I share this view, that the FDA is acting prematurely. As a personal note I would like to add that I have not been deterred by the black box warning from a continued use of pimecrolimus, and neither have my patients or their parents. Long-term studies designed to look into this issue are either planned or are already ongoing.

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The Use of Lasers in the Pediatric Population

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ABSTRACT

Over the past 2 decades, there have been numerous advances in laser therapy of birthmarks in the pediatric population. Concerns regarding efficacy, overall benefit, and side-effects linger. We present our opinion, based upon decades of clinical experience, on the role of lasers to treat port wine stains, superficial hemangiomas, and café au lait macules in children.
Key Words: *hemangioma, café au lait macules, pediatrics*

Port Wine Stains

Port wine stains (PWSs) are congenital vascular malformations composed of ectatic capillary-like vessels in the papillary dermis that occur in 0.3% of newborns. They can vary in size (millimeters to >50% body surface area) and color (flat pink patches to "cobblestoned" purple plaques) as the patient ages. Children with PWSs should be treated early to prevent adverse sequelae to their psychological development.

Observable reduction in PWS size and color is achieved through laser therapy by selective vascular damage. The pulsed dye laser (PDL) is the laser of choice due to its low risk of scarring or pigmentary alteration[1,2] and relatively high rates of clearing.

Which Laser Is Best for Children?

In one study, use of the 595nm PDL with 1.5msec pulse width and fluences up to 11-12J/cm^2 with a dynamic cooling spray resulted in >75% clearance of PWSs in 63% of patients under the age of 12 months, after four treatments.[3] Lack of controlled trials with single parameter variation make it difficult to ascertain optimal settings in this area. The addition of a dynamic cryogen cooling device (DCD) has advanced the treatment of PWSs by allowing for epidermal protection via surface cooling and resultant heat accumulation in vessels. Recently Bernstein and Brown, using the 585nm PDL with DCD at a 1.5msec pulse duration, demonstrated an average 68% subjective and 69% objective improvement in 83 previously untreated PWSs after approximately four treatments.[4] Additional devices, including the 1064nm Nd:YAG are now also being tested for PWS combination treatment.[5]

We routinely start with the largest available spot size (10mm), a pulse duration of 1.5msec, and fluence of 7.5J/cm^2 with the V-Beam laser (Candela) and then, depending on the outcome, we may reduce the spot size to 7.0mm and vary the fluence from 9-14J/cm^2 or 6-8.5J/cm^2 with the V-Star laser (Cynosure). Treated tissue should appear dark purple but not assume a grayish hue, which may indicate potential overtreatment. This temporary purpura may last 7-10 days.

Will It Work?

Certain favorable prognostic features are known about PWSs. We advocate early treatment; success is likely due to thinner skin in infants, as well as smaller and more superficial vessels leading to improved clearance in fewer treatment sessions.[6] Based on current studies, >50% improvement has been reported after an average of four treatments per patient.[3,4,7]

Pearls	Pitfalls
• Mark treatment site because reactive erythema often clouds otherwise distinct borders. • Treat edge of PWS first to prevent inadvertent treatment of unaffected adjacent skin. • Aim the laser tangentially to the skin surface when treating central areas to avoid the uneven, lattice-like appearance of partially treated areas.[8] • For darker skin types, waiting as long as 3 months between treatment sessions is recommended to permit postinflammatory hyperpigmentation, if present, to resolve.	• The risk of hypertrophic and atrophic scarring exists but is extraordinarily low. Cutaneous atrophy that may rarely appear within 1-2 months following PDL treatment usually resolves within a 3- to 18-month period. • In dark-skinned individuals, epidermal sloughing can develop following treatment, requiring wound care and leading to pigmentary change. • Clearance is location dependent (see next page).

Table 1: Use of the PDL to treat port wine stains

Red lesions appear to clear more with the PDL than pink or purple lesions and lesions on the head and neck respond more favorably than those on the trunk and lower extremities. Furthermore, the midline facial area responds better than the lateral face and neck.

PWSs rarely clear completely even with a series of treatments, but optimal improvement is usually achieved with repeat sessions every 4-8 weeks. PWSs may respond, (to a lesser degree) in skin types IV and V with lower fluences and multiple treatments, though the risk of pigmentary alteration is more common than that in lighter skin tones (see Table 1).

Superficial Hemangiomas

Superficial hemangiomas are benign proliferations of endothelial tissue with an incidence of almost 10% by the age of 1 year. They are frequently located on the head or neck and if not present at birth, usually appear shortly thereafter, showing a female-to-male predominance. The natural history of these hemangiomas has two phases, proliferating (marked by significant growth during the first 7 months of life) and involuting (pallor within the lesion followed by involution and residual atrophic telangiectatic skin with fibrofatty tissue in some cases). Complications such as ulceration, obstruction of vital structures, and recurrent bleeding can occur. Laser therapy can prevent such complications and provide psychological relief for pediatric patients and their parents during the first few years of life. Early treatment reduces the chance that the lesion will reach its full size and minimizes the risk of fibrofatty tissue development.

Which Laser Is Best for Children?

The short-pulsed (0.45-1.5msec) PDL (either 585nm or 595nm) with dynamic or air cooling is the treatment of choice for hemangiomas comprised mostly of superficial vessels.[9] Since the depth of selective photothermolysis with the 585nm PDL is 1.2mm, deeper components of hemangiomas may progress. Better results are often achieved with larger spot sizes (7mm, 10mm).[10] Newer long-pulsed Nd:YAG lasers may be more effective but further study is necessary.

Will It Work?

Although opinions differ regarding the treatment of hemangiomas in patients younger than 4 months old[11] (as hemangiomas may spontaneously resolve within the first year of life), long-term studies have not been carried out using objective observers nor have data regarding significant improvement vs. clearance been reported. We advocate early intervention given the minimal risks associated with laser therapy and the notion that the most effective time for treatment is during the proliferation phase. Some evidence suggests lesions less than 3mm may resolve better than thicker lesions.[12] As in treatment of PWSs, the basic principles of depth and size apply to efficacy of laser therapy. Multiple treatments may be needed to achieve maximal clearing and are recommended to begin during the rapid proliferating phase in 2-3 week intervals. During the involuting phase, treatments can be spread out to every 1-2 months.

Ulceration and subsequent pain is a frequent complication in 5%-14% of all infantile hemangiomas and though compelling data do not exist to support the use of a single therapy,[13] faster rates of resolution may occur with the PDL[14,15] than with Nd:YAG lasers, potentially due to increasing rates of reepithelialization. In our practice, we always start with biologic dressings and add PDL if this fails.

Café au Lait Macules

Café au lait macules (CALMs) are benign hyperpigmented areas, present at birth in 2% of all newborns (up to 1/3 of black neonates).[16] While they can be markers for underlying disease such as neurofibromatosis, isolated CALMs are recognized as a common finding in many infants and may increase in size over time. The exact etiology of the macules is unknown. Cosmetic improvement can be achieved by use of any of the short-pulsed lasers which selectively destroy melanosomes.

Which Laser Is Best for Children?

Laser therapy for CALMs is considered safe but there is no data to suggest that treatment of CALMs in infancy is required. The best choice is the Q-switched pigment-specific laser. Efficacy studies on the Q-switched Nd:YAG lasers (532nm or 1064nm), the Q-switched alexandrite (755nm), and the Q-switched ruby laser (694nm) show that each of these lasers works with varying degrees of efficacy;[17] to date no study comparing the Q-switched lasers has been carried out. Wheeland and Schmults[18] recommend the Q-switched

Pearls	Pitfalls
• Best for non-tan skin phototypes I – III. • Topical or intradermal local anesthetics are often required. • All children and their parents should be given laser-specific optically coated glasses. • Always determine treatment parameters with a test spot, which should be evaluated after 4-8 weeks. • Begin with the lowest energy fluence that produces a visible response. Do not overlap areas.	• Hyperpigmentation can occur, but usually improves with the passage of time or the application of topical bleaching creams. • Risk of hypopigmentation is higher with the Q-switched ruby laser than for the Q-switched alexandrite and the Q-switched Nd:YAG at 1064.[19] • The area may appear abraded after treatment. Wound care should be started and continued until the area is completely reepithelialized. Treatment area should heal within 5-14 days.

Table 2: Use of Q-switched lasers to treat café au lait macules

532nm Nd:YAG laser, though it is worth mentioning that the risk of purpura and postoperative abradement of the treated area may be unacceptable to parents of pediatric patients.

Will It Work?

Clinical experience with repeated Q-switched laser treatments has been inconsistent, with total clearing occurring in approximately 50% of patients and recurrence and patchy pigmentation occurring in the other half.[19] The risk of repigmentation exists for all CALMs though the mechanism behind this is unknown. It appears that if total clearing is achieved repigmentation is rare, though an exact percentage has not been uniformly reported. The key to successful treatment is to use relatively low fluences and perform multiple treatment sessions 6-8 weeks apart. It is generally agreed that results seen at 12 months after the last treatment are usually lasting.[20,21] Given the risk of pigmentary alteration, skin types IV-VI should generally not be treated, as CALMs are often less apparent and the risk of pigment change outweighs cosmesis. In all skin types, the risk of postinflammatory hypopigmentation exists, and if this occurs, a delay in further treatments until the pigmentation normalizes is recommended (see Table 2).

Conclusion

While additional long-term studies may be needed to assess the efficacy of laser therapy in the pediatric population, our experience suggests that laser use in children for the treatment of port wine stains, superficial hemangiomas, and café au lait macules has not only been well tolerated by patients but also successful with minimal side-effects.

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Class	Name/Company	Approval Dates and Comments
Antibacterial Agent	**Tigecycline** *Tygacil*™ Wyeth Pharmaceuticals	The US FDA approved this novel IV antibiotic in June 2005 for the treatment of complicated skin and skin structure infections in adults. It has a broad spectrum of antimicrobial activity, including activity against the drug-resistant bacterium methicillin-resistant *Staphylococcus aureus.*
Antifungal Agent	**Terbinafine HCl** *Lamisil® Tablets* Ranbaxy Laboratories	The US FDA gave tentative approval to manufacture and market this antifungal agent in June 2005 for the treatment of onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium). Product launch is expected after the US FDA gives their final approval.
Antibacterial Agent	**Moxifloxacin HCl** *Avelox®* Schering-Plough	The US FDA approved this once-daily antibiotic in June 2005 for the treatment of complicated skin and skin structure infections in adults that are caused by methicillin-susceptible *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae,* or *Enterobacter cloacae*.
Monoclonal Antibody	**Adalimumab** *Humira®* Abbott Laboratories	The EMEA issued a positive opinion in June 2005, recommending approval of this monoclonal antibody for the treatment of psoriatic arthritis.

Drug News	
Research Results	In an article published in the June issue of the *Journal of the Federation of American Societies for Experimental Biology** scientists reported that dithranol, which is used for the treatment of severe psoriasis, induces keratinocyte apoptosis through a novel mitochondrial pathway dependent on oxidative respiration and involving electron transfer with the ubiquinone pool. They suggested that this could be a potentially important mechanism involved in the clearance of psoriasis.* **FASEB J* 19(8):1012-4 (2005 Jun).
Insect Repellant	According to a recent report in *The Medical Letter**, Picaridin (KBR 3023) became available in June 2005 in the US as a 7% solution (Cutter Advanced®, Spectrum Brands). Picaridin has been used as an insect repellant for years in Europe and Australia, where no serious toxicity has been reported. The US Centers for Disease Control and Prevention is recommending it as an alternative to DEET. Repellants containing picaridin are not registered for use in Canada. **The Medical Letter* 47(1210):46-7 (2005 Jun 6).
Drug Warning	Skin Cap® (Cheminova Laboratories International SA) is a product made in Madrid, Spain that was sold in the US in the mid-1990s. Its active ingredients were reported to be pyrithione zinc and sodium lauryl sulfate. However, analysis of two lots of this product demonstrated that it also contained clobetasol propionate. In 1997, the US FDA stopped its importation into the US. In 2004, a sample purchased over the internet was again analyzed showing adulteration with high-potency glucocorticosteroids.* **Arch Dermatol* 141(6):801-3 (2005 Jun).

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