(Intro Slide)

Major Head	Pramosone® -- An Alternative for Breaking the Itch-Scratch Cycle in Dermatitis
Subhead(s)	(names of authors) (sponsor) (presenter)

Major Head Dermatitis/Eczema

Subhead Chronic, relapsing inflammatory skin disease characterized by:

- pruritus
- excoriations
- erythema
- erosions
- lichenification
- papules
- dry skin

Notes

In the past dermatitis was used to describe skin diseases of known external causation, such as “contact dermatitis” and “allergic dermatitis.” The term “eczema” was reserved for skin inflammation that had no apparent external cause, for example atopic dermatitis. Today the terms “eczema” and “dermatitis” are used interchangeably.

All forms of dermatitis are characterized to some degree by pruritus, excoriations, erythema, erosions, lichenification, papules, and dry skin.

IIa

Major Head Atopic Dermatitis

Subhead Characteristics:

- Familial course
- Often coexists with other atopic diseases (rhinitis, asthma, allergic conjunctivitis)
- Barrier defect
- Poorly understood immune pathology

Notes

The causes of atopic dermatitis are poorly understood. A hereditary component is unmistakable, since the disease tends to run in families and coexists with other atopic diseases such as rhinitis, asthma, and allergic conjunctivitis.

One theory holds that atopic dermatitis results from a defect in lipid biosynthesis resulting in weakening of the epidermal barrier. When this occurs skin loses fluid, and irritants can enter the skin more easily, exacerbating the condition.

The immune pathology of dermatitis has not been clearly elucidated either. We know that skin lesions are infiltrated with basophils, eosinophils, T cells, and mononuclear phagocytes. Between 60% and 80% of patients with atopic dermatitis show elevated IgE levels, and usually have elevated eosinophils.

Major Head Prevalence and Economics

Subhead Quantifying prevalence is difficult.

However:

- 20% of infants and young children show symptoms
- 60% continue to have one or more symptoms of AD into adulthood
- 90% develop symptoms before age 5
- Intermittent relapses into adulthood
- Atopic dermatitis affects about 15 million Americans, or about 5%, at any one time[1]
- Insurers spend about $1 billion on AD
- Early intervention may favorably affect overall outcome

Notes Quantifying the incidence and occurrence of atopic dermatitis is difficult. About 20% of all infants show symptoms at some point, with 90% of those presenting the first symptoms by age five. Of those, about 60% continue to be affected into adulthood.

Atopic dermatitis affects about 15 million Americans, or about 5% of all Americans at any one time. Healthcare costs associated with atopic dermatitis are in the range of about $1 billion.

[1] National Institute of Arthritis and Musculoskeletal and Skin Diseases. Health Topics. Handout on health: atopic dermatitis. http://www.niams.nih.gov/hi/topics/dermatitis/index.html#link_b. Accessed August 25, 2003.

Major Head

Other common types of eczema

- Allergic contact dermatitis (eczema)
- Irritant contact dermatitis (eczema)
- Dyshidrotic eczema
- Neurodermatitis
- Nummular eczema
- Seborrheic dermatitis/eczema

Notes

Other types of eczema or dermatitis listed here include allergic eczema, dyshidrotic eczema, neurodermatitis, nummular eczema, and seborrheic eczema.

Two slides

[photos of AD/eczema]

(I can write notes for these if material is provided)

Major Head Treating AD

Subhead Goals: skin healing, flare prevention, breaking the itch-scratch cycle

Subhead Treatment options

- Emolients
- Topical, systemic steroids
- Topical immunomodulators
- Topical steroid + immune modulators

- Antihistamines
- Antibiotics
- Immune suppressants
- Phototherapy (ultraviolet A or B)

Emolients represent the first-line treatment for inflammatory skin diseases. Topical corticosteroid creams and ointments have also been used for decades to treat these disorders and are still the most-used agents. Immune modulator agents help control inflammation while reducing immune system reactions. Examples of these agents are tacrolimus ointment and pimecrolimus cream. Immune modulators help to reduce flares and may lower the need for long-term treatment with steroids.

Later in this presentation you will learn about the benefits of combination therapies that include an appropriate topical steroid plus an immunomodulator, and how the benefits of these two agents can be further enhanced with the right vehicle.

Ancillary treatments for atopic dermatitis, used with steroids and/or immune modulators, include antihistamines, antibiotics, and immune suppressants. Ultraviolet light has been used to reduce the need for topical steroids but by itself is not very effective in treating inflammatory skin diseases. Possible long-term effects of UV therapy are premature skin aging and skin cancer.

Major Head Itch-Scratch Cycle

- Patients often identify pruritus a the worst symptom
- Scratching releases inflammatory compounds into skin
- Excoriations allow greater opportunity for infection and/or skin drying

Notes

Pruritus is the most common symptom of atopic dermatitis and eczema, and one which many patients identify as the most difficult to deal with. Scratching, the natural response to pruritus, is the major factor in the “chicken and egg” phenomenon known as the “itch-scratch cycle.” Scratching usually continuesuntil it induces pain . The latter is mediated through the same nerves as itching, and appears to be more bearable to the patient than the persistent itching.

Scratching by itself helps to summon inflammatory mediators to the skin, which increases inflammation and pruritus. Resulting excoriations increase the likelihood of infection and provide an easy avenue for bacterial toxins to enter the wound. Toxins of *Staphylococcus aureus*, which colonizes the skin of many atopic dermatitis patients, can increase the inflammatory response at the wound site and further dry the skin.

Goals of topical anti-inflammatory therapy should therefore be to break the itch-scratch cycle and restore barrier integrity.

Major Head Pramosone®

Subhead Another option for breaking the itch-scratch cycle

- Hydrocortisone acetate, 1% or 2.5%, plus pramoxine hydrochloride 1%
- Cream, lotion ointment
- Anti-inflammatory steroid plus pramoxine, an anesthetic

Pramosone represents another option in treating atopic dermatitis, especially in patients who have difficulty breaking the itch-scratch cycle. Consisting of low-potency hydrocortisone acetate and pramoxine, a topical anesthetic, Pramosone offers mild anti-inflammatory activity plus relief of itching. Pramosone is worth considering for patients with mild atopic dermatitis who are prone, due to itching, to exacerbate their condition. Pramosone is also used to treat allergic dermatitis, insect bites, neurodermatitis, and is suitable for undefined itching or for post-scabies or post-laser treatment.

Slide 8

Major Head Topical Steroids

Graphic Chemical structure of hydrocortisone acetate.

Notes

For decades, topical steroids have been the mainstay treatment for atopic dermatitis. Since the introduction of hydrocortisone in the early 1950s, a variety of new agents have been developed with a range of potencies.

This slide shows the basic hydrocortisone skeleton. Hydrocortisone has a single bond between carbons 1 and 2, hydrogens at the 6 and 9 positions, and hydroxy groups on C-17 and C-21. Over the years medicinal chemists have modified this basic structure in dozens of ways in their search for more potent agents. Chemical modifications include adding a double bond between carbons 1 and 2, halogenation (with fluorine or chlorine) at C6 and/or C9, and adding ester groups at C-17 and C-21. Hydrocortisone 17-butyrate, for example, is the ester formed between butyric acid and the C-17 hydroxyl group of hydrocortisone.

Many modifications to thehydrocortisone skeleton increased efficacy, but at the expense of safety . Fluorination, for example, resulted in very high-potency steroids, but increased efficacy was offset by dramatic increases in the risk for both topical and systemic adverse events.

Major Head Potency Classification for Topical Steroids

[Reproduce Slide GIS 130.012]
[Need a reference: I could not find one]

Notes

This classification system for topical steroids is familiar to most dermatologists. In this scheme, products classified as I are considered "super potent" in eczema and psoriasis, while those in class VII are "least potent." This classification accounts for steroid potency as well as the influence of the base on potency. However, it does not distinguish anti-inflammatory from anti-mitotic effects.

We'll see a lot more about the subject of delivery vehicle in later slides. For now note that mometasone furoate ointment is classified as a "two," or very potent agent, while the cream formulation of the same steroid lies in the middle of the potency classification scheme. Similarly, betamethasone valerate cream is two levels less potent than betamethasone ointment.

This slide suggests that the delivery vehicle can profoundly affect steroid potency and perhaps patient outcome as well.

Major Head Potency Correlates with Vasoconstriction

Subhead Stoughton vasoconstriction assay

- Steroid potency/efficacy in psoriasis correlates with vasoconstriction[2]
- Vasoconstriction and active concentration correlate poorly[3]
- Generic formulations not as potent as name brands (?)[4]
- Vasoconstriction only a rough estimate of potency[5]

Notes Steroid potency correlates with vasoconstriction, as Stoughton has shown in numerous studies. However, sometimes vasoconstriction does not coincide with clinical observations. For example, Stoughton observed that more-potent formulations of the same steroid agent do not always give a higher vasoconstriction value. Similarly, according to Stoughton generic formulations may not be as potent as name brand steroids. Recently, a study by XXX suggests that vasoconstriction is a poor predictor of steroid potency, which means that at some point we may see another revision of the potency tables.

(I need a reference here: either recent articles in Archives of Dermatology etc. that say vasoconstrictor assay gives a rough estimate, but doesn't always agree with clinical observation or a relevant passage from Fitzpatrick, *Dermatology in General Medicine*)

[2] Cornell RC, Stoughton RB. Correlation of the vasoconstriction assay and clinical activity in psoriasis. *Arch Dermatol*. (1985)121:63-67.
[3] Stoughton RB, Wullick K. The same glucocorticoid in brand-name products. Does increasing the concentration result in greater topical biologic activity? *Arch Dermatol*. (1989) 125:1509-1511.
[4] Stoughton RB. Are generic formulations equivalent to trade-name topical glucocorticosteroids? *Arch Dermatol.* (1987) 123:1312-1314.
[5] Reference to be supplied

Major Head Pharmacology

Subhead Steroids work through intracellular steroid receptors in skin cells to inhibit production of inflammatory mediators.[6] However, the precise mode of action is poorly understood.

- Absorbed through skin, dependent on treatment area
- Halogenation increases lipophilicity, hence absorption

Subhead Local effects

- Anti-inflammatory activity
- Anti-mitotic effect
- Inhibition of collagen synthesis

Notes

The effects of topical steroids are mediated through steroid receptors in the cytoplasm of skin cells. Receptor affinity is apparently strengthened by halogenation , esterification, or both. This effect probably results from increased lipophilicity, and hence better skin absorption, imparted by these chemical substituents.

Anti-inflammatory effects arise from local vasoconstriction resulting from inhibition of the inflammatory cascade. Anti-mitotic activity and collagen synthesis inhibition in fibroblasts arise from inhibition of protein synthesis. Anti-mitotic and anti-collagen effects are important in hyperproliferative conditions like atopic dermatitis and psoriasis, whereas anti-inflammatory effects carry greater therapeutic consequence in other types of eczema.

[6] Royal Pharmaceutical Society of Great Britain. *The Pharmaceutical Journal* (online). PJ practice checklist: OTC steroids for eczema and dermatitis. http://www.pharmj.com/pdf/checklist/eczema.pdf. Accessed August 27, 2003.

Major Head

Guidelines for Treating with Topical Steroids[7]

- Match potency to disease severity
- Use the least potent steroid necessary
- Very potent steroids should not be used without specialist advice in children
- Monitor patients using moderate and potent steroids for local and systemic side effects
- Never use more than 50 grams of a potent steroid per week per patient

Notes

Topical steroids can treat a wide range of inflammatory skin diseases but safety is a concern, especially with the more potent agents and in children. The British Association of Dermatologists recommends these guidelines for topical steroids. In summary: always use the least potent steroid necessary and match potency to disease severity. This may require a step-up or step-down approach. Very potent steroids should not be used in children without specialist supervision, and all use of potent agents use must be accompanied by monitoring for local and systemic side effects. The Association also recommends not using more than 50 grams of a potent steroid per week on any individual patient.

[7] British Association of Dermatologists. Guidelines for the management of atopic eczema. Principles of treatment with topical steroids. http://www.bad.org.uk/doctors/service%20provision/Primary/eczema.htm. Accessed August 28, 2003

Major Head Safety of Topical Steroids

Subhead Topical Adverse Events

- Atrophy
- Striae
- Teleangiectasia

Subhead Systemic Events

- Suppression of HPA axis

Notes

For patients on long-term therapy, topical safety is of particular concern. While steroids are valuable in inflammatory and hyperproliferative skin diseases, they carry risks of topical adverse events such as dermal atrophy, striae, and teleangiectasia. The risk for topical adverse events is higher with halogenated compounds than with non-halogenated steroids.

Systemically, topical steroids can suppress function of the hypothalamic-pituitary-adrenal system, known as the HPA axis, especially after long-term use. Anti-HPA activity is a direct consequence of steroid pharmacokinetics, as we will see in the next slide.

Major Head Safety of Topical Steroids

Subhead Plasma Half-Life

Agent	PHL (minutes)
hydrocortisone	90
hydrocortisone 17-butyrate (LOCOID)	90-120
methylprednisolone	>200
triamcinolone	>200
betamethasone-17-valerate	>300
dexamethasone	>300

(the entries in yellow must be highlighted somehow on the slide)

Notes

To reduce interference with the HPA axis, steroids must penetrate minimally to systemic circulation, and once there these agents need to be metabolized quickly – preferably to non-active metabolites. Halogenated compounds (either chlorinated or fluorinated) are metabolically stable. Consequently, they exhibit considerably longer plasma half-lives than non-halogenated agents do. In this slide, the highlighted steroids are halogenated, whereas the non-highlighted agents contain no halogens.

Studies measuring the effect of topical steroids on the HPA axis clearly indicate a lower risk of systemic adverse events with non-halogenated steroids such as hydrocortisone and hydrocortisone 17-butyrate.

Major Head Safety of Hydrocortisone 17-butyrate

Subhead Adrenal Suppression (*Visscher et al*[8])

- Fatty cream hydrocortisone 17-butyrate 0.1% vs. fatty cream mometasone furoate 0.1%
- Open-lable crossover design over 30 days
- 12 healthy male volunteers

- Both agents suppressed adrenal function, as measured by lower plasma cortisol levels
- Mometasone effect significantly stronger ($P = 0.0220$)
- Transient effects for both agents

Notes Visscher and coworkers compared the adrenal safety of a fatty cream formulation of hydrocortisone 17-butyrate with that of a similarly formulated mometasone furoate. Investigators found that both agents suppressed adrenal funcation, as measured by lower plasma cortisol levels. This effect was significantly stronger for mometasone furoate. However, the adrenal suppressive effects for both agents were transitory, returning to baseline levels approximately 8 days after therapy.

[We could use at least one slide of recent studies showing topical steroid safety]

[8] Visscher HW, Ebels JT, Roders GA, Jonkman JGH. Randomized crossover comparison of adrenal suppressive effects of dermal creams containing glucocorticosteroids. *Eur J Clin Pharmacol* (1995) 48:123-125.

Major Head Efficacy of Hydrocortisone 17-butyrate

Subhead Pediatric efficacy (and safety?): (*Schachner*[9])

- Double-blind; 30 patients: 9 months to 17 years old
- Hydrocortisone 17-butyrate (Locoid®) vs. vehicle
- Medications applied twice daily
- Patients assessed at baseline and 3, 7, and 14 days
- Statistically significant improvement for Locoid® vs. vehichle by day 3 in all categories ($p < 0.03$ to 0.003),
- Efficacy maximized by day 14, when all efficacy parameters reached 0.001 statistical significance
- Potential for downgrading to less potent steroid possible at 72 hours

Notes

A double-blind pediatric efficacy study by Schachner tested Locoid® **[formulation?]** versus vehicle in 30 pediatric patients. Patients were given two tubes of medication and instructed on which side of their body to apply them. Patients were assessed at day 3, 7, and 14 for typical manifestations of atopic dermatitis, including erythema, scaling, vesiculation, oozing, lichenification, crusting, and pruritis.

All patients were initially rated as "severe" or "very severe." Notable improvement was noted by day three, with statistical significance ranging from the level of $p < 0.03$ for pururitis and erythema to the 0.004 level for oozing, with an overall rating of 0.003 at day 3. By day three all patients had improved to the moderate severity range. Investigators concluded from the high day-three efficacy that clinicians could perhaps switch pediatric patients at this point to a less potent steroid.

By day 14 all efficacy parameters for Locoid® exceeded those of vehicle alone, to the $p < 0.001$ level of significance.

[9] Schachner LA. A 3-day rate of efficacy of a moderate potency topical steroid in the treatment of atopic dermatitis in infancy and childhood. *Pediatric Dermatol* (1996) 13:513-514.

Major Head Hydrocortisone 17-butyrate
Locoid®

[graphic: chemical structure from slide 30.015]

Notes The chemical structure of hydrocortisone 17-butyrate, the active ingredient in LOCOID, is the basis of this molecule's favorable pharmacology. You'll notice the lack of the double bond between carbons 1 and 2, no fluorination at C6 and/or C9, and the butyrate ester at C17. After absorption into the skin, hydrocortisone 17-butyrate is de-esterified to hydrocortisone and inactive butyric acid.

Major Head	Hydrocortisone 17-butyrate (Locoid®)
Subhead	Excellent benefit/safety ratio
Text Box	Efficacy
Text (below box)	Potent as halogenated steroids
Text Box **(put alongside "Efficacy")**	Safety
Text (below box)	Comparable to hydrocortisone

(see slide 16 for guidance)

Notes

These chemical features put hydrocortisone 17-butyrate right in the middle of the potency scale, with the fluorinated steroids like betamethasone, triamcinolone, and fluocinolone. However, because hydrocortisone 17-butyrate is rapidly metabolized to hydrocortisone and inert butyric acid, the systemic safety of this agent is equal to that of natural hydrocortisone. One could say that hydrocortisone 17-butyrate's favorable efficacy/safety ratio represents the best qualities of high-potency agents with safety comparable to that of hydrocortisone.

Major Head The Vehicle Difference

Graphic (reproduce slide 29: “Types of dermatological vehicles.” Remove “acute WET conditions,” arrow, and “chronic DRY conditions” and place on following slide)

Notes The most effective topical therapies take advantages of both the active ingredient and the delivery vehicle. Everyone understands that different topical actives have widely varying potencies, but the effect of vehicle is often under-appreciated. In addition to supplying the mechanical means of delivering active to affected areas, vehicles offer a separate healing benefit if chosen correctly.

Unlike actives, which carry a measurable benefit/risk ratio, that ratio for delivery vehicles is almost always high.

This slide shows the familiar breakdown of topical vehicles by type. The three corners of the vehicle triangle represent powder, wet liquid formulations, and oily or greasy preparations.

Major Head Vehicle Appropriateness

Graphic (reproduce everything below the bottom of the triangle from slide 29)

Table Head Variety in skin lesions

Table

	Acute, weeping	Chronic, dry
Occurrence	20-30%	70-80%
Prescription patterns	50-80% creams	20-50% ointments

Notes The conventional wisdom “wet on wet, oil on dry” has served dermatologists and patients alike. Creams are used in acute, weeping conditions while ointments are more suitable for chronic, dry conditions. This advice is not strictly followed in practice. While weeping skin disease is indeed treated more than half the time with creams, dermatologists prescribe ointments somewhat less than half of the time for chronic, dry conditions for which this vehicle provides the most benefit.

Apart from lotions used to treat hairy body regions, creams are prescribed 80% of the time in some countries.

[note: It would be nice to have a reference for either prescribing habits or relative efficacies of creams/ointments in various conditions]

Major Head Why prescribing patterns do not follow the "rule"

Subhead *Skin conditions often call for ointments, but patents prefer creams for cosmetic reasons*

Sub-subhead nevertheless…

- Vehicle as important as active
- Barrier function of stratum corneum is crucial in maintaining water balance

Notes Patients prefer creams for cosmetic reasons. Ointments are perceived as "dirty," even though they are more effective in treating dry skin.

The need for better formulations are based on the importance of vehicle and of maintaining barrier function, as well as patients' formulation preferences.

Major Head Transepidermal water loss (TEWL)

Graphic (use graphic from slide 32)

Notes

This simplified representation of the outer epidermal layer depicts minimal trans-epidermal water loss, or TEWL, as an important factor in maintenance of optimal skin hydration. When barrier function becomes impaired through damage to the intercellular lipid layers of the stratum corneum, the skin becomes more sensitive to disease, especially in atopic individuals. Thereofre, restoring skin barrier function is essential for healing.

Electrical conductance experiments have shown that pure petrolatum increases skin hydration compared with untreated skin. As can be expected, a great deal of variation is observed in various topical formulations, depending on the vehicle's fatty content.

The conclusion here is that ointments occlude better than creams, but the story is actually more complicated.

Major Head Fatty Cream “Lipocream®” Formulation

Graphic (slide 35)

Notes

Creams are composed typically of 30% oil in a 70% water base, whereas ointments have feature 30% water in 70% oil. A new formulation created by Brocades Pharma in **[when?]**, the so-called “fatty cream” or Lipocream formulation, uses 70% oil in a water base.

This idea may seem like double talk, since Lipocream contains the same gross fractions of oil and water as a typical ointment. However, there is quite a difference between the two formulations. Ointments are oil-based, meaning that the formulation begins with oil into which water is dispersed up to about 30% by weight. In the fatty cream or Lipocream formulation, water is the base. Oil is added and dispersed as in a cream, but the oil loading is much higher than for creams. Lipocream therefore combines the appearance and feel of a cream, with the therapeutic benefits of an oil-based ointment. The result is a vehicle that patients prefer, but which provides restoration of barrier function.

REVISE

Major Head The Three Ps of Steroid Phobia

- Patients
- Physicians
- Parents

Notes Steroid phobia is common among patients, physicians, and parents of pediatric patients. Patients and parents hear the word “steroid” and are immediately worried about side effects, primarily immune suppression and skin atrophy. Even physicians who routinely prescribe systemic prednisone for asthma may hesitate to prescribe anything more potent than Class VII topical steroids for atopic dermatitis. Although research indeed supports the careful use of the most potent steroids, especially halogenated agents, the mid-potency non-halogenated steroids have an exemplary safety record.
[need more information on this – reference?]

Major Head Locoid®: Range of formulations

Table

Formulation	Application/benefit
Locoid cream	acute, weeping dermatoses non-greasy, invisible after application
Locoid ointment	hyperproliferative, lichenified lesions
Locoid Lipocream®	subacute to chronic, dry lesions; 70% oil in water base
Locoid lotion	hairy areas

Notes

[Note: we need more information on what these formulations consist of]

In treating dry skin dermatoses, there is a great need for agents that provide efficacy, safety, restoration of skin barrier function, and cosmetic appeal. The Locoid range of products fulfills these needs by providing a safe, mid-potency steroid in a vehicle most appropriate to the condition and area on the body which is affected.

Major Head

Modern Approaches to Treating Atopic Dermatitis/Eczema

- Delivery vehicles – first-line therapy, may be as important as active
- Topical steroids remain the treatment of choice but concerns over side effects
- Immunomodulators (tacrolimus, pimecrolimus) perceived as safe, but slow onset and annoying side effects
- Steroids plus immunomodulators provide high safety, low risk, higher efficacy, and greater versatility

Notes

Earlier we briefly examined strategies for treating atopic dermatitis and related skin disorders. Topical strategies are outlined in this slide.

The right delivery vehicle is considered first-line therapy. Topical steroids in an appropriate vehicle are still the treatment of choice in many instances. For many patients, however, the topical calcineurin inhibitors tacrolimus and pimecrolimus, also known as topical immunomodulators or "TIMs," have changed inflammatory skin disease management by providing higher safety and, in many cases, equivalent efficacy.

Combination therapy that includes a topical steroid plus a topical immunomodulator offers the benefits of both agents while minimizing each treatment's drawbacks.

Major Head Immunomodulators in Atopic Dermatitis

- Immune dysfunction underlies atopic dermatitis
- Organ-specificity implies organ-specific signs
- Treating symptoms vs. underlying disorder
- Topical immunomodulators: another means of addressing the inflammatory response

Notes

Atopic dermatitis is typical of diseases involving an over-responsive immune system. The manifestations of atopic dermatitis are believed to be organ-specific, just as with other inflammatory diseases. For example wheezing and shortness of breath are characteristic breathing disorders, as is itching and redness for atopic skin disease. It comes as no surprise that patients with atopic dermatitis are often asthmatic as well.

For years, treating atopic or allergic diseases involved providing symptomatic relief of these organ-specific symptoms. As the inflammatory response became better understood, anti-inflammatory corticosteroids took their rightful place as agents for treating both immediate symptoms and the underlying causes of atopic dermatitis.

Most recently, topical immunomodulators have emerged as agents for controlling the immune response. Like topical steroids, TIMs are believed to work on the underlying immune response.

Major Head Immunomodulators

Subhead Cyclosporine: Powerful, systemic immune suppression

- Use limited to severe, unresponsive AD
- Serious immune suppression, eg to prevent organ transplantation rejection
- Poor topical absorption, so must be administered systemically

Subhead Dermatologic topical immunomodulators (TIMs)

Tacrolimus
  - fungus-derived antibiotic
  - has been used systemically
  - topical formulation approved for AD
  - little systemic penetration

Notes Like cyclosporine, tacrolimus, acalcineurin inhibitor, is a fungus-derived antibiotic originally used to prevent organ rejection in transplantation medicine. Tacrolimus has been shown to be effective as an oral medication for refractory atopic dermatitis, psoriasis, and acute contact dermatitis. Topical tacrolimus ointment, which was approved for treating atopic dermatitis, was the first new treatment for atopic dermatitis in many years.

In placebo-controlled trials involving nearly 8,000 patients, topical tacrolimus improved or cleared more than 60% of atopic dermatitis conditions.

Because tacrolimus does not appear to enter the bloodstream to any appreciable degree, this agent is less likely to cause systemic effects. Side effects are principally dermatolotic and include burning, stinging, itching and infrequently a blistering rash, all of which appear to improve along with the dermatitis.

Major Head TIMs used in Dermatology

- Tacrolimus – Protopic ointment 0.03%, 0.1%
- Pimecrolimus – Elidel™ cream 1%

- bacterial-derived antibiotics/calcineurin inhibitors
- strong systemic immune suppressants
- low penetration, especially in thick skin, than steroids[10]

Notes Tacrolimus, which in dermatology goes by the trade name Protopic, is a powerful immune suppressant used in organ transplantation. Tacrolimus was the first significant non-steroid topical agent approved for atopic dermatitis in more than 50 years. Pimecrolimus cream, or Elidel, is a related compound with similar mode of action.

Because of its large molecular weight, 822, tacrolimus does not penetrate skin as well as topical steroids. Similarly pimecrolimus, with a molecular weight of 810, is poorly absorbed into the skin. Perhaps for this reason neither drug is associated with skin atrophy, which is considered their major safety feature.

[10] Nghiem P, Pearson G, Langley RG. Tacrolimus and pimecrolimus: from clever prokaryotes to inhibiting calcineurin and treating atopic dermatitis. *J Am Acad Dermatol.* (2002) 46:228-41.

Major Head TIMs vs. Steroids in Dermatology

Property	TIMs	Steroids
Onset	Delayed	Rapid
Typical steroidal side effects?	No	Yes
Long-term safety	Good	Variable
Disease management	Variable	Excellent
Skin irritation (stinging/burning)	15-40%	Relieve irritation

TIMs have changed management of atopic dermatitis and related skin diseases for the better. TIMs are often touted for their safety and quality of life benefits, especially when compared with potent steroids. However, many practitioners perceive steroids as providing better long-term patient outcomes.

On the surface, the two agents appear to be complementary in most important categories. TIMs have a somewhat slower onset of action. Because they are nonsteroidal and work through novel mechamisms, TIMs do not induce typical steroidal side effects such as atrophy, striae, and teleangiectasia, and these agents apparently show better long-term safety. However, as many as 40% of patients experience skin irritation early in TIM therapy, which may be relieved by topical steroids.

In practice, steroids and TIMs may be used together in a variety of regimens **[name these, references?]** that take advantage of the benefits of both agents, while minimizing each individual treatment's drawbacks.

Major Head Tacrolimus vs. Hydrocortisone Butyrate: Safety and Efficacy

Subhead *Reitamo et al[11]: two doses of tacrolimus ointment vs. vehicle-controlled hydrocortisone butyrate*

- 3-week, multicenter, randomized, double-blind, parallel-group study in 570 patients
- 0.03% and 1% tacrolimus vs. 0.1% hydrocortisone butyrate
- endpoint: mEASI mean AUC as percentage of baseline

Subhead Results

- lower improvement for 0.03% T vs. 0.1% T ($P < .001$) or 0.1% HCB ($P < .002$)
- T groups showed higher skin burning and pruritis than HCB group (0.05)
- Efficacy of 0.1% T and 0.1% HCB not statistically different
- No significant safety issues with either treatment

Notes Reitamo et al conducted a randomized, double-blind study in 570 patients to compare the relative safety and efficacy of two doses of tacrolimus ointment with that of 0.1% hydrocortisone 17-butyrate. In this three-week study, tacrolimus 0.1% was more effective than the same drug at 0.03% strength, but just as effective as 0.1% hydrocortisone butyrate. As expected, the tacrolimus-treated groups showed higher skin irritation and itching than the hydrocortisone butyrate-treated subjects.

[11] Reitamo S et al. Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone butyrate ointment in adult patients with atopic dermatitis. *J Allergy Clin Immunol* 109; 547-555 (200?)

Major Head Tacrolimus: Not the Complete Answer

- TIMs: generally safe, but annoying side effects and slow onset
- Steroids: effective, short onset, extensive experience, may mitigate side effects of TIMs
- Considering side effects, safety, and efficacy together, co-therapy may be the answer for many patients

Notes

Tacrolimus is safe and effective but its side effects – stinging, burning, itching – can be troublesome for some patients. Since side effects may persist for several days before patients notice improvement, compliance may be a problem.

Although topical steroid safety is no longer a real issue, dermatologists and patients alike remain concerned with long-term use, or any application to the face or other sensitive areas.

For many patients, combination therapy consisting of tacrolimus, steroid, and an appropriate agent provides the best combination of safety and efficacy. Co-therapy delivers favorable safety-to-risk, improved rate of onset compared with tacrolimus alone, and minimizes steroid side effects. In short, co-therapy offers patients the therapeutic benefits of both TIMs and steroids, while minimizing the safety issues of both agents.

Major Head TIMs and Topical Steroids

Subhead Complimentary efficacies, side effects

- TIMs used on facial areas to eliminate risk of skin atrophy, but slow onset
- Steroids reduce severity of TIM burning, stinging, and are faster-acting

Subhead Strategies

- Substitute one agent with another
- Co-therapy (alternating, simultaneous)

Notes

The complimentary efficacies and safety profiles of TIMs and topical corticosteroids present interesting therapeutic possibilities. With the advent of picrolemus and pimecrolemus, dermatologists and patients need not fear the side effects, particularly skin atrophy, associated with treating facial dermatitis with mid-potency steroids. TIMs present no such risk.

On the other hand dermatologists who prefer TIMs over steroids can often mitigate the burning and itching associated with TIMs by prescribing a short course of mid-potency steroid, for example hydrocortisone 17-butyrate, at the beginning of therapy. Steroid pre-treatment can greatly minimize the uncomfortable side-effects of TIMs.

Finally, the availability of both treatments offers the opportunity to switch from one type of agent to another based on individual patient response. Another strategy, which we will examine in more detail in subsequent slides, is to combine sequentially or together.

Major Head

Pilot Study: hydrocortisone butyrate 0.1% lipocream + tacrolimus 1% ointment

Subhead

Study design:

- Open-label, single-center, four-week trial
- Nine patients with atopic dermatitis who had experienced irritation with tacrolimus
- Patients used tacrolimus 0.1% ointment and hydrocortisone butyrate 0.1% lipocream twice daily **[What was the exact regimen? First…second…third…fourth? Together?]**
- Clinical evaluation at baseline, day 3, week 1, week 2, week 4
- Primary endpoint: investigator global assessment (IGA) of disease status
- Patients asked to evaluate irritation experienced with earlier tacrolimus treatment

Notes

A pilot study by Lebwohl **[reference]** investigated the use of hydrocortisone butyrate 0.1% Lipocream formulation plus tacrolimus 1% ointment in nine patients with atopic dermatitis. During this four-week trial patients were instructed to apply tacrolimus and hydrocortisone butyrate twice a day **[regimen?]**.

At the beginning of the study patients were asked to assess their irritation when earlier treated with tacrolimus alone.

Clinical evaluation was made at baseline, day three, and weeks 1, 2, and 4. The primary endpoint, investigator global assessment, IGA, was based on erythema, edema/population, excoriation, oozing/weeping/crusting, scaling, and lichenification using a severity scale graded from zero (none) to three (severe).

Major Head Pilot Study: hydrocortisone butyrate 0.1% lipocream + tacrolimus 1% ointment

Subhead Results: Irritation

Irritation

	None	Mild	Moderate	Severe
# Patients (single-agent)	0	2	3	4
# Patients (day 3, co-therapy)	5	4		
# Patients (4 weeks, co-therapy)	9			

$p = 0.0039$

All patients experienced irritation with prior single-agent tacrolimus therapy, as indicated in the table above, with almost half assessing their level of irritation as “severe.” At day three of co-therapy, four patients described their irritation as “mild” and five related no irritation at all. After nine weeks of treatment none of the patients evaluated were experiencing any treatment-related side-effects.

Compared with baseline irritation scores, results at day three and at the final visit were both statistically significant.

Major Head Pilot Study: hydrocortisone butyrate 0.1% lipocream + tacrolimus 1% ointment

Subhead Results: Efficacy

- Percent BSA at baseline: 18%
- Percent BSA at 4 weeks: 4%
- Mean decrease in BSA of 83.4% ($p < 0.0001$)
- IGA improved for all patients: $p = 0.0078$ (day 3), 0.0039 (week 4)
- No atrophy or telangiectasia

Notes Similarly encouraging results were obtained for efficacy. Patients exhibited a mean involvement of 18% of body surface area at baseline. All patients either improved or remained stable during the study period. The average BSA after four weeks of treatment was 4%, a decrease of 83.4%, which was highly statistically significant.

Investigator assessment also improved during the study, both at three days and as determined during the final visit. No patients experienced atrophy or teangiectasia.

Major Head	Compliance and Quality of Life
	Points: (please fill in)
Notes	(I will write these based on information from client)

Major Head

Conclusions

- Steroids: Rumors of my death are premature
- Versatility of mid-potency steroids: hydrocortisone 17-butyrate
- Importance of vehicle: Locoid
- TIMs first breakthrough in 50 years
- Steroid plus TIM offer better control of symptoms, fewer side effects, higher safety than either agent alone

Notes

In concluding this program I would like to leave you with these important messages. Topical corticosteroids remain the most widely used agents for treating atopic dermatitis. For safety reasons, many dermatologists prefer mid-potency steroids, for example hydrocortisone 17-butyrate, which offer a very favorable benefit-to-safety profile.

As for vehicle, patients often prefer creams even when ointments provide the most benefit. The solution may be one of the Locoid formulations, Locoid Lipocream, which combines the appearance and feel of a cream with the therapeutic benefits of an oil-based ointment.

Topical immunomodulators, the first new agents for treating atopic dermatitis in the past 50 years, have changed the way dermatologists manage this disease. Since many patients experience uncomfortable side effects with TIMs, especially early in treatment, many dermatologists today are using combination therapies that combine mid-potency steroids and TIMs. Since these two agents compliment one another in both efficacy and side effect profile, you could say that combination therapy represents the best of both worlds.

Miscellaneous:

Tables/study sent 9/4 do not address compliance, plus study only use 3 AD patients

Other missing information: Endogenus + exogenous repair info