Pediatric Advisory Committee Topical Tacrolimus Ointment (Protopic®)

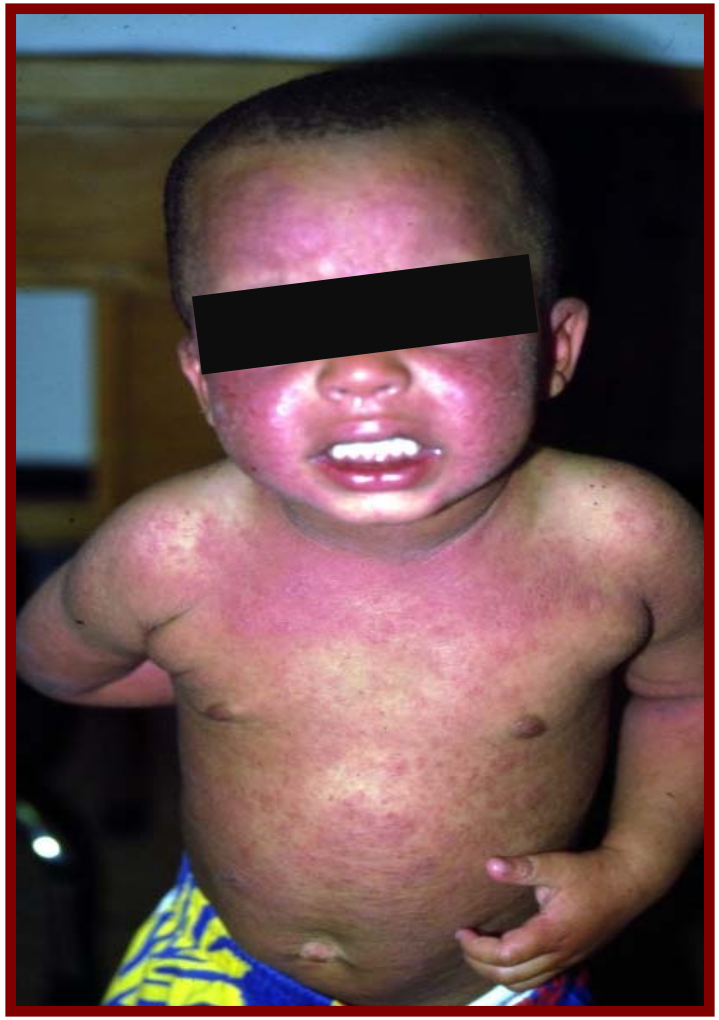
Astellas

May 16, 2011

Participants

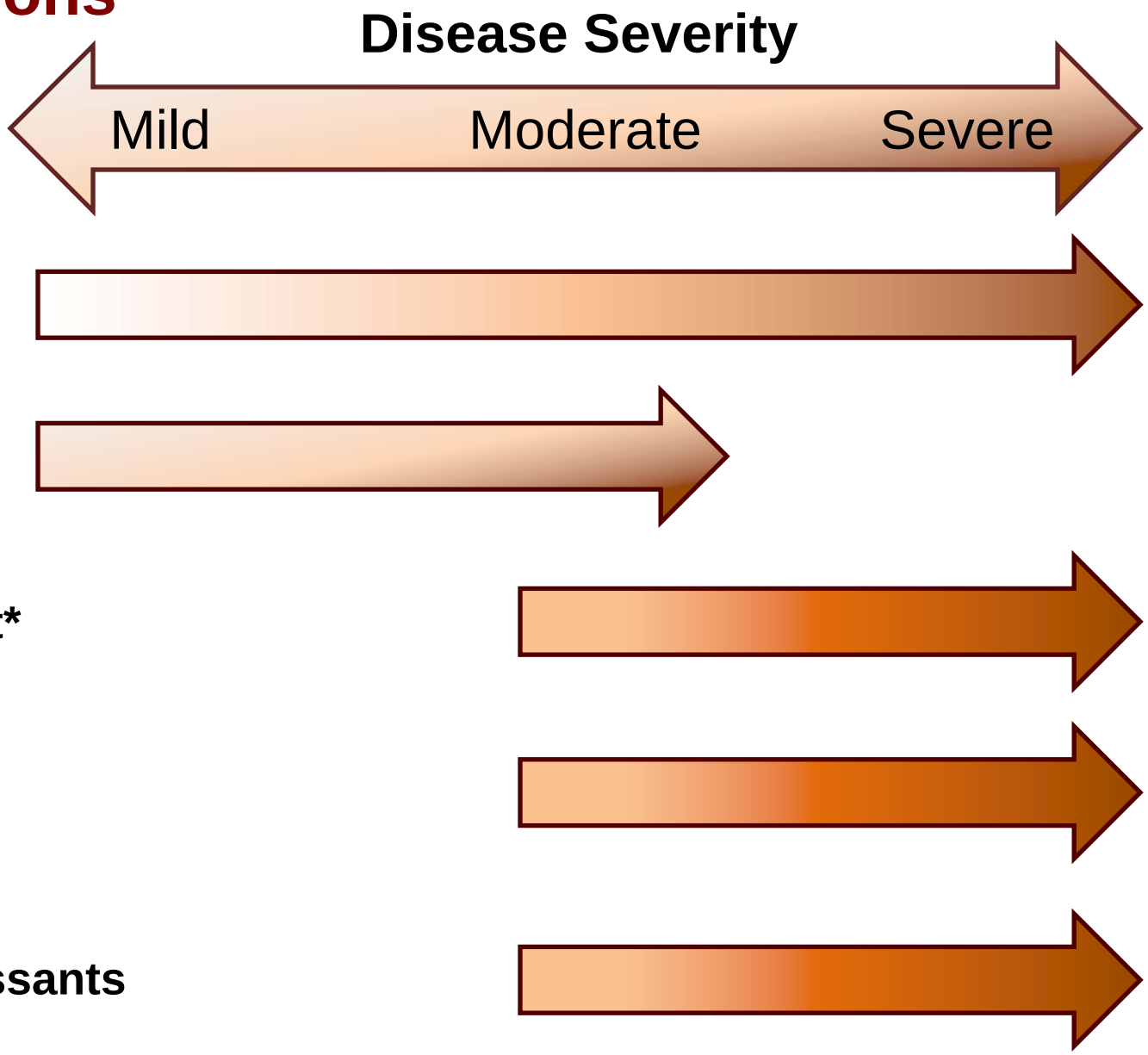
- Presenter
  - Joyce Rico, MD, MBA, Vice President, Medical Affairs, Astellas Pharma Global Development, Inc.
- Available consultant
  - Peter Heald, MD, Emeritus Professor of Dermatology, Yale University, School of Medicine, DSMB “APPLES”

Atopic Dermatitis



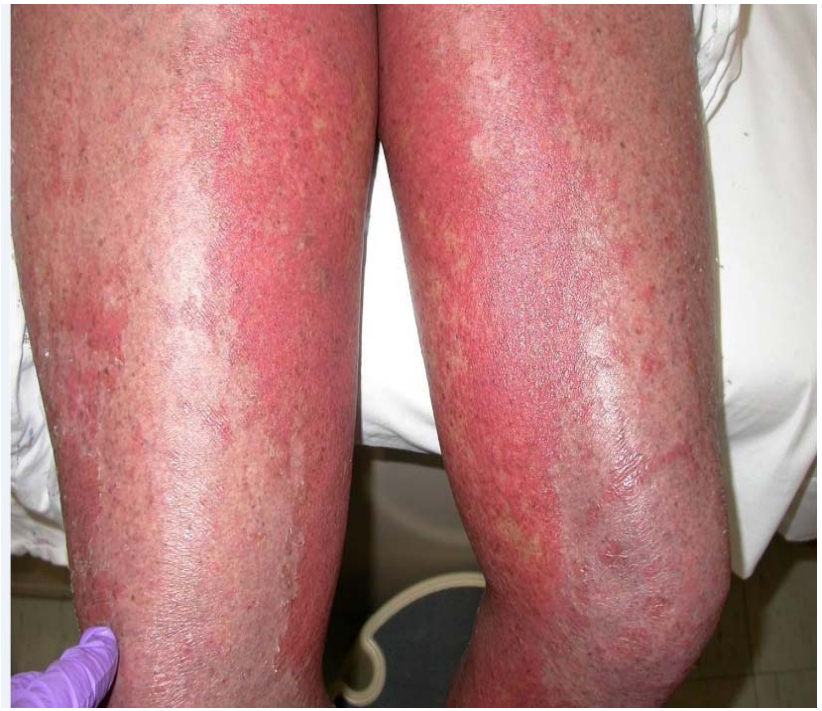
- Intensely itchy, relapsing skin disease which affects up to 20% of school age children
- Co-morbidities include: increased risk for cutaneous infections, asthma, hay fever, conjunctivitis
- Moderate-severe atopic dermatitis (AD) is a life-altering, inflammatory skin disease
- Significant impact on quality of life

Treatment Options



* 2nd line, non-immunocompromised patients

Cutaneous T Cell Lymphoma (CTCL)



- Rare T cell malignancy of skin-homing lymphocytes
- Intensely itchy, relapsing and refractory, often presents as eczematous dermatitis, misdiagnosed as AD
- Widespread cutaneous involvement
- Mycosis Fungoides (MF) most common form
- Skin biopsies often not diagnostic
- Clinical symptoms for years prior to diagnosis

CTCL and Dermatitis

- Adults with chronic recalcitrant eczematous dermatitis at increased risk of diagnosis of CTCL
  - Mean time from onset of symptoms to diagnosis of CTCL (Mycosis fungoides) is ~ 6 - 15 years
- Symptomatic treatment, often including Protopic, does not halt progression of disease

Epidemiologic Literature: Considerations

*"Study results suggest the possibility of an association between TAC and an increased risk of t-cell lymphoma, however causality is difficult to determine in light of the potential study biases"**

- Misclassification: Diagnostic codes are non-discriminatory
- Protopathic bias: Occurs when a pharmaceutical agent is inadvertently prescribed for an early manifestation of a disease that has not yet been diagnosed
- Confounding by indication: Indication for treatment (severe AD) may be related to the risk of diagnosis of T cell lymphoma (MF)

*** FDA Addendum: Update on CNI Pediatric Literature Review, May 10, 2011**

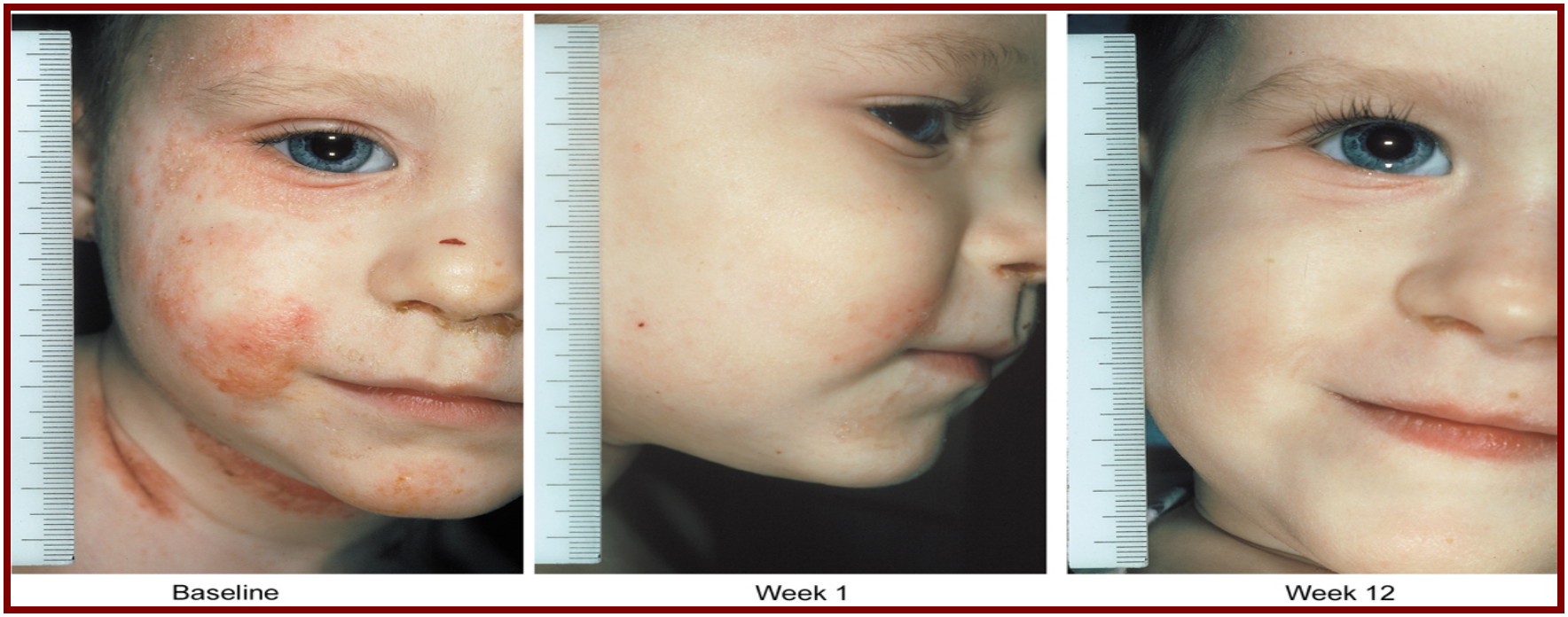
T Cell Lymphoma Signal
Not Consistent with Immunosuppression Data

- Tacrolimus is neither a mutagen nor carcinogen
- Animal studies with Protopic [dermal; 2 year]
  - Malignant lymphoma: Predominantly B cell
  - Mice systemic exposure [AUC]: 26 fold higher than maximum human dose
- Transplant patients with systemic immunosuppressants
  - Post transplant lymphoproliferative disease: B cell, EBV+
  - Risk factors: intensity and duration of immuno-suppression

Systemic Exposure Low in Protopic® Treated Patients

- Below limit of quantification in >90% of treated pediatric patients
- When present, blood levels were low, transient and occurred early in treatment
- Exposure in pediatric and adult patients is comparable
- In long term studies, average use was 0.6-2.2 g per day
- No evidence of systemic immunosuppression or impaired immune responses with Protopic

Protopic® is Effective for Moderate-Severe AD



- Clinical development program included 27,000 patients (9,000 pediatric patients)
- More effective than mid-low potency steroids or vehicle: 90% improvement from baseline, decrease in % BSA affected, EASI score, time to relapse and QOL

Source for Photo: Paller A, J Am Acad Dermatol 2001

Conclusions

- Protopic is effective for treating moderate to severe AD
- Observational studies support an association between chronic dermatitis and T cell lymphoma, most likely MF
  - Bias, misclassification, and confounders limit interpretation
- Although a causal relationship has not been established, labeling informs prescribers and patients on the potential risk of malignancy, specifically skin and lymphoma, including CTCL
- Astellas is committed to continuing to assess the safety of Protopic including the completion of the long term prospective registry in pediatric AD patients