SAFETY OF SYSTEMIC THERAPY IN PEDIATRIC DERMATOLOGY
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DISCLOSURES

- Consultant
  - Regeneron / Sanofi / Genzyme
  - Abbvie
  - Allobane
  - Eli Lilly
  - Galderma, Johnson & Johnson, (Omed), Theraplex
  - Pierre Fabre
  - Micros

- Speaker
  - Regeneron / Sanofi / Genzyme
  - Pierre Fabre
  - Pfizer

- Advisory Board Member
  - Regeneron / Sanofi / Genzyme
  - Abbvie
  - Dermira
  - Eli Lilly
  - Galderma, Johnson & Johnson, (Omed), Theraplex
  - IntraDerm and Realm Therapeutics
  - Pfizer

- Investigator
  - Regeneron / Sanofi / Genzyme
  - Abbvie
  - ABiome

ORPHANS...

- Very few systemic agents approved in children
- "They are not just little adults"... but they sort of are!
- They get severe skin disease too!

ATOPIC DERMATITIS

- For mild cases: simple approach can suffice
  - "Use this when you need it"
- For moderate and severe, this doesn’t work
  - "But I ALWAYS need it!"
- Poor outcomes:
  - Failure to adhere to the regimens
  - Under treatment
  - Side effects, including topical steroid withdrawal

Comparison of psoriasis and atopic dermatitis guidelines—an argument for aggressive atopic dermatitis management
Mary E. Lohse, BA  |  Peter A. Lio, MD

Aggressive nature of modern psoriasis treatment. AD guidelines include an assessment of quality of life but do not designate a disease severity threshold for systemic treatment. AD and psoriasis have a tremendous effect on quality of life. The AD guidelines have a less aggressive approach to disease management than the psoriasis guidelines. We should think critically about rapid advancement to systemic agents in AD management, especially now that more and better agents are being developed.
**SYSTEMIC TREATMENT ALGORITHM**

- **Cyclosporine** (5mg/kg)
  - 4-12 months
  - Phototherapy
  - Mycophenolate
  - Methotrexate
  - Azathioprine

**SYSTEMICS**

- Cyclosporine is my favorite – and is the favorite of most
- But there are real risks:
  - Hypertension, kidney damage, monthly blood work, tremor, hypertrichosis, gum hypertrophy... and cancer/infection risk

**CSA**

- Rapid
- 5mg/kg/d, 300mg/d max
- Monitoring: BP q wk x 4 then q mo CBC, LFTs, CMP, uric acid, lipids monthly x 3 then q 8 wks
- Maintain x 3 mo then taper
- Limit to 1 year
- *(Pediatric Dermatology Research Alliance)*

**CYCLOSPORINE: HOW?**


**MYCOPHENOLATE**

- Onset: 1-2 months
- I prefer to use this once better to maintain
- 40-60 mg/kg/d, 3 g/d max
- Can use concurrent prednisone or Cyclosporine x 1 mo
- Monitoring: CBC, CMP at 1 month then q month; LFTs q 3 months
- Limit to 2 years

**AZATHIOPRINE**

- Onset: 4-6 weeks
- Can use concurrent prednisone x 1 mo
- Baseline TPMT if normal: 2.5-3.5 mg/kg/d
- Intermediate TPMT: 1mg/kg/d
- Monitoring: CBC, LFTs, CMP at 2,4,8,12 weeks then q 8 weeks
- Maintain x 3 mo then taper
- Limit to 2 years
- (Pediatric Dermatology Research Alliance)

**METHOTREXATE**

- Baseline CBC and CMP + Hep panel
- 0.5mg/kg start, max 25mg po q wk
- Recheck at 1 week then q 4-6 weeks
- Start supplementation with folate 1mg qd

**METHOTREXATE**

Tips:
- Consider Silybum Marianum (milk thistle 250mg po bid) to protect liver [Neuman et al., Clin Biochem 1999]
- For nausea:
- Divide dose to separate into AM/PM
- Acupressure device at PC-6
- Ginger root/snaps
METHOTREXATE

• In the words of Dr. Jon Hanifin: “I keep trying it, but it never seems to work.”

MTX VS. CSA

• Low-dose MTX (7.5mg/week) vs. low-dose CsA (2.5 mg/kg/day) in 40 children with severe AD
• At 12 weeks, groups were indistinguishable, both about 50% improved


CSA VS. MYCOPHENOLATE

• 55 pts with AD rec’d CsA (5mg/kg/d) for 6 weeks; then they either rec’d CsA (3mg/kg/d) or Mycophenolate (1440 mg)
• At 10 weeks, low-dose CsA and Mycophenolate were comparable, but mycophenolate was slower


PREDNISONE?

DUPILUMAB

• A human monoclonal antibody against IL-4 receptor alpha
• Inhibits signaling of IL-4 and IL-13
• FDA approved for moderate-severe AD in adults initially
• Injected SC every 2 weeks

DUPILUMAB

• 671 patients in SOLO 1 and 708 in SOLO 2 trials
• SOLO 1: primary outcome* occurred in 38% vs 10% of placebo (P<0.001).

*SIV 0/1 with at least a 2 point reduction at week 16

DUPILUMAB

It appears much safer than conventional immunosuppressants, but there are other potential considerations:
- Conjunctivitis in up to 10%
- Injection site reaction/systemic reactions
- Cost may be a factor
- Injection
- Adults initially...

ADOLESCENT DATA

- 12-17 yo mod-to-severe AD, 1:1:1 placebo, 300 mg sq q4 wk, or 200/300 mg sq q2 wk
- For most endpoints, q2w regimen was superior to q4w regimen
- Safety profile was acceptable: conjunctivitis and injection-site reactions were higher vs. placebo, but AD exacerbation and non-herpetic skin infections were lower vs. placebo
- Both placebo-corrected efficacy and safety of dupilumab in adolescents were similar to those in adults

Simpson et al. Dupilumab Efficacy and Safety in Adolescents with Moderate-to-Severe Atopic Dermatitis: Results from a Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel-Group, Phase 3 Study. EADV Presentation, September 2018.
Remission?


Table 1: Characteristics of patients with remitent effect following Dupilumab discontinuation

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WHAT IF DUPILUMAB IS NOT ENOUGH?

American Journal of Clinical Dermatology
https://doi.org/10.1007/s40257-019-00436-8

THERAPY IN PRACTICE

Management Recommendations for Dupilumab Partial and Non-durable Responders in Atopic Dermatitis

Aleksi J. Hendricks1 - Peter A. Lio1,2, Vivian Y. Shi2

Dupilumab

500 mg subcutaneously every 2 weeks (maintenance dose)

Partial and non-durable responders in atopic dermatitis

10 weeks

Add additional immunosuppressive agent

Consider oral corticosteroids

Add systemic immunosuppressive agent

Add topical corticosteroids

Consider systemic immunosuppressive agent

Remitent group

Partial and non-durable responders in atopic dermatitis

Stay on dupilumab


PSORIASIS

• Methotrexate and phototherapy are the go-to treatments in children with more severe disease
• But there are other options now
• Etanercept is the only approved biologic agent for pediatric psoriasis at this time

DOXYCYCLINE

• “For more than half a century, the tetracycline class of antibiotics has been limited in use to children 8 years of age or older except for treatment of life-threatening indications without other treatment options (e.g., Rocky Mountain spotted fever). The limited use was based on warnings in package inserts related to the chelation with calcium in bones and tooth enamel.”
DOXYCYCLINE

- "Clinical studies have demonstrated that doxycycline may be used safely in pediatric patients <8 years of age for short-term use without concerns of tooth discoloration or weakening of the tooth enamel. A recommendation by the AAP states that doxycycline may be used for up to 21 days regardless of the patient's age."
- "The AAP and Centers for Disease Control and Prevention recommend doxycycline as the drug of choice for treatment of rickettsial disease in patients of all ages."

CONCLUSIONS

- Children are not little adults, but they can suffer just the same
- Though we may never get specific therapies approved, we must continue to work to help children with severe dermatologic disease
- By working together and sharing our knowledge, we can take care of children safely and effectively

THANK YOU!