NATIONAL DERMATOLOGY RESIDENT LECTURE SERIES SUMMARY

Lecture: Atopic Dermatitis Therapeutic Updates by Dr. Aaron Wong
Date: April 14, 2020 via Zoom
Compiled by: Danny Mansour, PGY2, University of British Columbia

Hanafin and Rajka Criteria (this was presented in lecture, Bolognia has an adapted version)

Major – must have 3 or more	Minor – should have 3 or more
• Pruritus • Early age of onset • Typical morphology and distribution – flexural lichenification and linear distribution in adults, facial and extensor involvement during infancy and childhood • Chronic or chronically relapsing dermatitis • Personal or family history of atopy (asthma, allergic rhinoconjunctivitis, atopic dermatitis)	• Xerosis • Hand/foot non-specific dermatitis • Pityriasis alba • Nipple eczema • White dermatogtaphism • Subcapsular cataract • Increased serum IgE level • Immediate (type 1) skin response • Susceptibility to cutaneous infections (staph and HSV)

Janus Kinase (JAK) Inhibitors – JAK 1/2/3 and TYK2 (tyrosine kinase), called "Jakinibs"

Mechanism of Action	Pathway	Examples	Side Effects
• Complicated... • B cell increase class switching to IgE • Keratinocytes can increase IL-4 signaling • Increase IL-5 and thus increase eosinophil burden • Increase IL-31 → itch	• Receptor tyrosine kinase (RTK) promote activation of JAK • JAKs autophosphorylate and recruit Signal Transducers and Activators of Transcription (STAT) • Phosphorylated STAT proteins dimerize • The STAT dimer enters the nucleus where it binds to DNA • Activates gene transcription → regulating immunity, cell growth, and survival	• Oclacitinib – targets JAK1/2/3 for dog dermatitis • Tofacitinib – targets JAK1/2/3 • Ruxolitinib – targets JAK1/2 • Baricitinib – targets JAK1/2 • Upadacitinib – targets JAK1	• Cytopenias → JAK1/3 inhibition of IL2/4/7/9/15 • Increased lipids → JAK1/2 inhibition of IL-6 • Thrombolytic events → JAK2 inhibition of EPO, TPO etc. • Infections → JAK2/1 inhibition of IL-10 family type 2 gamma

Phosphodiesterase type IV (PDE4) Inhibitors – cleaves cAMP to AMP

Mechanism of Action	Examples
• Inhibits PDE4 thereby blocks cleavage of cAMP to AMP • <u>Atopic dermatitis skin:</u> high PDE4 levels → lower levels of cAMP → less protein kinase A (PKA) activation → increased nuclear factor of activated T-cells (NFAT) and nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) → INFLAMMATION • <u>Healthy skin:</u> low PDE4 levels → higher levels of cAMP → more PKA activation → less NFAT and NFkB → REDUCED INFLAMMATION	• Apremilast (Otezla) • Crisaborale (Eucrisa)

Lecture: Atopic Dermatitis Therapeutic Updates by Dr. Aaron Wong
Date: April 14, 2020 via Zoom
Compiled by: Danny Mansour, PGY2, University of British Columbia

Calcineurin Inhibitors

Mechanism of Action	Examples
• Block calcineurin → reduced activity of transcription factor NFAT-1 → decreased IL-2 • Tacrolimus and pimecrolimus both block FK506-binding protein which thereby inhibits calcineurin	• Cyclosporine • Tacrolimus – comes as 0.03% and 0.1% ointment, costs ~$100/30g tube, ~$200/60g • Pimecrolimus – comes as 1% cream, costs ~$100/30g tube, $200/60g

Combined IL-4 and IL-13 Inhibition (Dupilumab)

Background	Indications	Bloodwork	Treatment for Conjunctivitis
• Blocks IL-4R-alpha subunit which is located on both IL-4 and IL-13 receptor therefore blocking both IL-4 and IL-13 • Human monoclonal IgG4 antibody • Dosed 600mg SC and then 300mg q2weekly • Costs ~$2000 /month	• Dermatitis • Asthma • Chronic nasal polyps	• Typically none • You can do basic baseline work-up: CBC, LFTs, Cr etc.	• Stop drug • Lid hygiene • Warm compress • Artificial tears • Topical antihistamine • Steroid eyedrops • Compound cyclosporin eyedrops • Refer to ophthalmology if refractory to general measures

IL-31 and IL-13 Inhibition

IL-31 (plays a role in ITCH)	IL-13 (Th2 cytokine)
• Nemolizumab is an IL-31 receptor antagonist (IL-31Ralpha) dosed 0.5mg/kg q4 weeks for moderate to severe prurigo nodularis • BMS-981164—Bristol Meyers Squibb (drug company), in development	• Tralokinumab • Lebrikizumab

Other Pipeline Biologics

- IL-22 → Fezakizumab
- TSLP-OX40/IL-33 axis (thymic stromal lymphopoietin) → Tezepelumab
- IL-33 → Etokimab

Impetiginized Eczema – New Topical Therapy

- Ozenoxacin 1% is the newest commercially available topical for impetigo; used BID x5-7 days
- Effective against staphylococcus aureus (MSSA and MRSA) and streptococcus pyogenes
- Mechanism of Action
    - Bactericidal quinolone → inhibits DNA gyrase or topoisomerase IV, reducing DNA replication