IL-1 ILnesses:
From diagnosis to management of pyrexic, pustular and purulent dermatoses

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Dermatology Branch
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National Institutes of Health
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Conflicts of Interest

No financial conflicts of interest.

I am conducting an investigator-initiated clinical trial using anakinra to treat pustular dermatoses (NCT01794117).

I will be discussing off-label uses of pharmacological agents for the management of autoinflammatory diseases.
Autoimmune diseases

Autoinflammatory diseases

- Rare monogenic autoinflammatory diseases
  - CAPS, DIRA, DITRA
- Mixed pattern diseases
  - Behcets, some vasculitides
- Rare monogenic autoimmune diseases
  - ALPS, IPEX, APECED

Classic polygenic autoinflammatory diseases
- Gout, Still’s dz

Classic polygenic autoimmune diseases
- SLE, dermatomyositis, scleroderma
IL-1β

- Pro-inflammatory cytokine
- Produced by myeloid cells
- Induces transcription of proinflammatory cytokines
- IL-1 receptor type 1 (IL-1R1) is ubiquitously expressed
- Synthesis and release are tightly regulated
- Also regulated by IL-1 receptor antagonist (IL-1RA)
## Monogenic Autoinflammatory Diseases

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Fabinon and Aksentivich. *Nat Rev Rheumatol* 2015;11
Cryopyrin Associated Periodic Fever Syndromes (CAPS)

Mild
- Familial Cold Autoinflammatory Syndrome (FCAS)
- Muckle-Wells Syndrome (MWS)
- Neonatal Onset Multifocal Inflammatory Disease (NOMID)

Severe

Clinical features
- Fevers
- Neutrophilic urticaria
- Conjunctivitis
- Arthralgias
- Leukocytosis
- ↑ Inflammatory markers
- CNS/cochlear inflammation
- Bone lesions
NLRP3 Mutations

Beer HD, et al. *JID* 2014; 134
IL-1 antagonists

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<th>Drug</th>
<th>Half-life</th>
<th>Dose</th>
<th>Administration</th>
<th>Indications</th>
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<tr>
<td>Ilaris (Canakinumab)</td>
<td>$t_{1/2} = 26$ days</td>
<td>150mg</td>
<td>every 8 weeks</td>
<td>CAPS, sJIA</td>
</tr>
<tr>
<td>Kineret (Anakinra)</td>
<td>$t_{1/2} = 4-6$ hours</td>
<td>100mg</td>
<td>daily</td>
<td>RA, CAPS</td>
</tr>
<tr>
<td>Xoma 052 (Gevokizumab)</td>
<td>$t_{1/2} = 22$ days</td>
<td>60mg</td>
<td>every 4 weeks</td>
<td>(?uveitis, PG)</td>
</tr>
<tr>
<td>Arcalyst (Rilonacept)</td>
<td>$t_{1/2} = 8$ days</td>
<td>160mg</td>
<td>weekly</td>
<td>CAPS</td>
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Beer HD, et al. *JID*; 2014; 134
Neutrophilic Urticaria

- Schnitzler syndrome
  - Neutrophilic urticaria
  - Fevers
  - Bony lesions
  - Monoclonal IgM

- Still’s disease/sJIA
  - Neutrophilic urticaria
  - Fevers
  - Arthritis
  - ↑ Ferritin

- Urticarial Vasculitis
  - Chronic urticaria
  - Arthralgias
  - Systemic involvement
  - Leukocytoclastic vasculitis

Eiling, et al. JAAD 2007;57
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Fabinon and Aksentivich. *Nat Rev Rheumatol* 2015;11
Pyogenic Arthritis, Pyoderma gangrenosum, Acne (PAPA)

- Autosomal dominant
- Incomplete penetrance
- Painful, recurrent, aseptic skin & joint inflammation
- Fevers
- 1st decade: aseptic monoarthritis (elbows, knees, ankles), neutrophilic infiltrate
- Puberty: severe acne, PG
- Skin involvement variable
- Pathergy
PSTPIP1 Mutations

Beer HD, et al. JID; 2014; 134
PAPA: Management

- Most consistent responses with TNFα antagonists
- Anakinra effective for joint >> skin
- Combination therapy with IL-1 antagonist + TNFα antagonist
- Systemic corticosteroids for joints may exacerbate acne

Cortis E, et al. *J Pediatrics* 2004;145
Smith EJ, et al. *Current Genomics* 2010;11
Tofteland ND, et al. *J Clin Rheumatol* 2010;16
PSTPIP1 mutations in isolated PG?

Mutations in the PSTPIP1 gene and aberrant splicing variants in patients with pyoderma gangrenosum


1. Splicing variants $\rightarrow$ frameshift mutations $\rightarrow$ premature stop codons $\rightarrow$ protein truncation
2. Novel G258A mutation, exon 11 $\rightarrow$ affects PSTPIP1 dimerization
3. Novel (CCTG)$_n$ tandem repeats in PSTPIP1 promoter

Clin Exp Derm 2011;36:889-895
Pyoderma Gangrenosum

Infliximab

Ustekinumab

Guenova E, et al. *Arch Derm* 2011;147
An open-label study of anakinra for the treatment of moderate to severe hidradenitis suppurativa

Leslie KS, et al. JAMA Dermatology 2014;70
Synovitis-Acne-Pustulosis-Hyperostosis-Osteitis (SAPHO) Syndrome

**Osteoarticular**
- Hyperostosis and osteitis
  - Anterior chest wall (65-90%)
  - Spinal involvement (30%)
  - Sacroiliitis

**Dermatologic**
- Palmoplantar pustulosis (60%)
- Severe acne vulgaris (25%, male)
- Follicular occlusion triad
- Generalized pustular psoriasis
- Psoriasis vulgaris
- Pyoderma gangrenosum
- Sweet syndrome

Jurik AG et al. *J Pediatric Orthop* 1988
Grosjean C et al. *J Rheumatology* 2010
Hurtado-Nedelec M et al. *J Rheumatology* 2010
Nguyen et al. *Semin Arthr Rheum* 2012
SAPHO: Management

• Therapy
  – Joint involvement
    – 1\textsuperscript{st} line: NSAIDs
    – 2\textsuperscript{nd} line: MTX vs bisphosphonates vs TNFα antagonist
  – Skin involvement
    – Systemic retinoids, methotrexate, cyclosporine
    – TNFα antagonist: infliximab, adalimumab, etanercept

Arias-Santiago et al. \textit{Acta Derm Venereol} 2010
Eleftheriou et al. \textit{Rheumatology} 2010
Anakinra treatment of SAPHO syndrome: short-term results of an open study

Table 1  Summary of the case reports

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age-sex</th>
<th>Disease duration (years)</th>
<th>Previous treatments</th>
<th>Skin involvement</th>
<th>Bone and joint involvement</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
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<tr>
<td>1</td>
<td>54-F</td>
<td>11</td>
<td>NSAIDs Prednisone MTX Lef LEF</td>
<td>PPP</td>
<td>Synovitis</td>
<td>Yes after 1 week; skin 100%; joint 80%</td>
<td>Injection site reaction; stopped after 10 days</td>
</tr>
<tr>
<td>2</td>
<td>41-M</td>
<td>23</td>
<td>NSAIDs Prednisone Colchicines SZP Retinoids</td>
<td>PPP</td>
<td>Osteitis (spine) Synovitis</td>
<td>Yes after 10 days; BASDAI 45 to 9; pain 80%; NSAIDs 50%; ESR 100 to 66</td>
<td>No AE</td>
</tr>
<tr>
<td>3</td>
<td>49-F</td>
<td>13</td>
<td>NSAIDs MTX Infliximab Retinoids</td>
<td>Hydradenitis</td>
<td>Synovitis</td>
<td>Yes after 15 days; pain synovitis; stop opioids</td>
<td>No AE</td>
</tr>
<tr>
<td>4</td>
<td>53-F</td>
<td>4</td>
<td>NSAIDs Prednisone MTX Colchicines Infliximab Etanercept Adalimumab</td>
<td>PPP and furunculosis</td>
<td>Osteitis (pelvis) Synovitis</td>
<td>Yes within 1 month; pain 70%; analgesics reduction; ESR 24 to 8</td>
<td>No AE</td>
</tr>
<tr>
<td>5</td>
<td>25-F</td>
<td>2</td>
<td>NSAIDs</td>
<td>PPP</td>
<td>Osteitis Hyperostosis (fibula) Synovitis</td>
<td>Yes after 15 days; pain 6.5 to 2; NSAID reduction</td>
<td>No AE</td>
</tr>
<tr>
<td>6</td>
<td>37-M</td>
<td>7</td>
<td>Pamidronate NSAIDs Pamidronate Adalimumab Etanercept</td>
<td>PPP</td>
<td>Osteitis Hyperostosis Sterno costo clavicular</td>
<td>No at 2 months</td>
<td>Transaminases $\times 1.5$</td>
</tr>
</tbody>
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AE, adverse event; ESR, erythrocyte sedimentation rate; F, female; LEF, leflunomide; M, male; MTX, methotrexate; NSAIDs, non-steroidal anti inflammatory drugs; PPP, palmoplantar pustulosis; SZP, sulfasalazine.
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**Deficiency of IL-1-receptor antagonist (DIRA)**
- **Gene**: IL1RN
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- **Mutation type**: Loss of function
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Fabinon and Aksentivich. *Nat Rev Rheumatol* 2015;11
Deficiency of the IL-1 Receptor Antagonist (DIRA)

- Onset birth-3 wks
- Fetal distress
- Joint swelling/pain
- Pustulosis
- Skeletal disease
  - Widening of rib ends (9/9)
  - Multifocal osteolytic lesions (8/9)
  - Heterotopic ossification (7/9)
- Stomatitis
- HSM

No high fevers; limited response to steroids
2 deaths: multi-organ failure 2/2 SIRS (2 & 21mo)
1 death: progressive interstitial fibrosis

IL-1 Receptor Antagonist Mutations

Beer HD, et al. JID 2014; 134
DIRA: response to treatment with Anakinra

Before anakinra  Anakinra x5 months

Interleukin-36–Receptor Antagonist Deficiency and Generalized Pustular Psoriasis

- Autosomal recessive, familial and sporadic
- Variable onset
- Acute flares of generalized pustular psoriasis, variable frequency
- Fevers, neutrophilia, leukocytosis, systemic inflammation, ↑CRP
- Death due to septicemia

IL-36Ra =
IL-36α =
IL-36β =
IL-36γ =

DIRA vs DITRA

IL36RN mutations

1. Phenotypic spectrum of disease
2. Account for a minority of pustular dermatoses
3. Distinguishing features

Early age of onset

Systemic inflammation \(\downarrow\) Psoriasis vulgaris

First Clinical Description of an Infant With Interleukin-36-Receptor Antagonist Deficiency Successfully Treated With Anakinra

Before Anakinra

Anakinra x 1 month

Lutz, Lipsker. *Arch Derm* March 2012
Pustular Skin Disease Study

Therapeutic trial using anakinra to treat inflammatory pustular skin diseases.

Enrolling participants who:
• Are men and women, age 18 and older.
• Are diagnosed with an active inflammatory pustular skin disease such as:
  • Acrodermatitis continua of Hallopeau
  • Generalized pustular psoriasis
  • Palmoplantar pustulosis
  • Palmoplantar pustular psoriasis
  • Subcorneal pustular dermatosis
  • Reactive arthritis
• Have a primary care physician.
• Will travel to the NIH Clinical Center during the 4-month study period.

Contact:
Haley Naik MD, (301) 594-3457, haley.naik@nih.gov
NLRP3 Inflammasome Complex

Beer HD, et al. JID; 2014; 134
Thank you

- Edward Cowen, MD MHSc
- Raphaella Goldbach-Mansky, MD
- Amanda Ombrello, MD
- Mark Udey, MD PhD

Phase 2 Study of Anakinra in Inflammatory Pustular Dermatoses

- www.clinicaltrials.gov
- haley.naik@nih.gov, 301-594-3457