Update on Pustular Psoriasis

Disclosures

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- Consultant for Clementia and Regeneron

Pustular Psoriasis

- Generalized Variants
  - Generalized Pustular Psoriasis

- Localized Variants
  - Localized pustular psoriasis
  - Acrodermatitis Continua of Hallopeau
  - Palmoplantar Pustulosis

Generalized Pustular Psoriasis (GPP)

- First documented by von Zumbusch in 1910
- An uncommon variant of psoriasis with acute onset that can present at any age
  - Estimated 0.6-0.7 cases per million people
  - Familial cases have been reported
- Appears to be more common in Hispanic and Asian populations
- Hallmark feature is erythema and sterile subcorneal pustulosis both clinically and histologically
  - It can appear with or without a previous history of psoriasis vulgaris

GPP (continued)

- Can see mucosal involvement
  - Geographic tongue
- Fever and systemic symptoms are common
  - Elevated WBC and ESR
- Can be life-threatening
  - Complications include:
    - ARDS
    - Pneumonia
    - CHF
    - Hepatitis
- Can reoccur in periodic episodes
Triggers for GPP

- Pregnancy (impetigo herpetiformis)
- Rapid tapering of corticosteroids (or other systemic therapies)
- Hypocalcemia
- Infections
- Sunlight/phototherapy
- Medications

Localized Pustular Psoriasis

- Pustules within or at the edge of an existing psoriatic plaque
- Can be seen in unstable forms of plaque psoriasis
- Also can occur after the application of topical irritants to a psoriasis plaque (e.g. tar or anthralin)

Acrodermatitis Continua of Hallopeau

- Rare and most often seen in middle aged females
- Pustules are seen on the dorsal portions of fingers/toes
- Involvement of the nail bed can occur and lead to shedding of the nail plate
- Generally affects a single digit
- May occur +/- psoriasis

Pathogenesis of Pustular Psoriasis

**The Role of IL-1 Family**

Cowen et al. Arch Derm 2012 Mar; 148(3): 381-4
IL-36 Signaling

Deficiency of the IL-1 Receptor Antagonist (DIRA)
- Onset birth-3 wks
- Pustulosis
- Joint swelling/pain
- Skeletal disease
  - Widening of rib ends
  - Multifocal osteolytic lesions
  - Heterotopic ossification
- No high fevers, limited response to steroids

Can be fatal with multi-organ failure 2/2 SIRS and progressive interstitial fibrosis

DIRA: Response to Treatment with Anakinra

Before anakinra
Anakinra x5 months

GPP Alone vs GPP with Psoriasis
- In a Japanese cohort, a majority of cases of GPP alone were associated with mutations in IL36RN
- This was in contrast to GPP with psoriasis, where only a small number of patients had IL36RN mutations
- Gain of function mutation in CARD14 implicated in the pathogenesis of GPP with psoriasis.
CARD14 in European Cohort

- A recent study looking at 863 pustular psoriasis patients in a European population, found that CARD14 mutations are observed in only a small minority of cases
- They did not detect any CARD14 substitutions in European patients with GPP

A New Gene Candidate – AP1S3


Studies strongly implicate IL-1 family in the pathophysiology of GPP

- However, multiple case reports demonstrate mixed results with IL-1B receptor antagonists, anakinra and canakinumab
- Further studies needed

Pustular Skin Disease Study

Therapeutic trial using anakinra to treat inflammatory pustular skin diseases.

Eligible participants:
- Men and women, age 18 and older.
- Diagnosed with an active inflammatory pustular skin disease such as:
  - Acrodermatitis continua of Hallopeau
  - Pustular psoriasis
  - Pustulopapular 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: Edward Cowen MD MHSc, coweng@mail.nih.gov or Haley Naik MD, haley.naik@ucsf.edu

Newer Biologics for Psoriasis in the Treatment of GPP

- Studies reveal improvement in GPP in a majority of patients treated with ustekinumab, brodalumab, secukinumab, and ixekizumab.
  - Maybe irrespective of IL36RN mutation status
BI-655130
- Humanised anti-IL36R monoclonal antibody
- Results from Phase 1 trial for moderate to severe GPP presented at the Inflammatory Skin Disease Summit in December 2018

Phase 1 Study Design

Demographics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>Race</th>
<th>Country</th>
<th>IL36RN Mutation Status</th>
<th>Initial GPPGA Score</th>
<th>Week 1 GPPGA Score</th>
<th>Week 2 GPPGA Score</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>47</td>
<td>M</td>
<td>WH</td>
<td>US</td>
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<td>1</td>
<td>1</td>
<td>1</td>
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<td>36</td>
<td>W</td>
<td>WH</td>
<td>US</td>
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<td>0</td>
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<td>3</td>
<td>26</td>
<td>M</td>
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<td>US</td>
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<td>1</td>
<td>0</td>
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<tr>
<td>4</td>
<td>25</td>
<td>W</td>
<td>WH</td>
<td>US</td>
<td>3</td>
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<td>5</td>
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<td>M</td>
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<td>US</td>
<td>3</td>
<td>1</td>
<td>0</td>
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</tr>
</tbody>
</table>

Efficacy
- Rapid clinical improvements were seen in all patients, irrespective of IL36RN mutation status
- A GPPGA score of 0 (clear) or 1 (almost clear) was achieved in 5 patients (71.4%) as early as Week 1, and in all patients by Week 4
- Within 48 hours, pustules were completely cleared in 3 patients (42.9%); pustules were cleared in 5 patients (71.4%) by Week 1 and in 6 patients (85.7%) by Week 2

Patient 2 and 4

Biomarker Analyses

A: CRP
B: Absolute neutrophil count
Transcriptome Analysis

- At baseline, global transcriptome analysis identified 3276 genes that were differentially expressed (1885 elevated; 1391 decreased) in lesional and non-lesional skin biopsies (adjusted p<0.05, fold-change≥2)
  - By Week 1, the expression of 1444 genes in lesional skin reached non-lesional levels
- At baseline, IL-36α, IL-36γ, and IL-8 gene expression was strongly elevated in lesional skin biopsies in all patients, by Week 1, IL36α and IL-36γ expression was strongly reduced in four patients, while IL-8 expression was strongly reduced in three patients (fold-change≥2)

Safety Through Week 20

<table>
<thead>
<tr>
<th>Adverse event (%)</th>
<th>No. of patients (n=52)</th>
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<tbody>
<tr>
<td>Arthralgia</td>
<td>7 (13.5)</td>
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<tr>
<td>Dry dermatitis</td>
<td>4 (7.7)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Hair</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Mucosa involvement</td>
<td>1 (1.9)</td>
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<tr>
<td>Throat infection</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Hibiscus-related</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>All deaths due to exacerbation of multi-drug 0</td>
<td></td>
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<tr>
<td>Dosing regimen</td>
<td>0</td>
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</table>

Palmoplantar Pustulosis (PPP)

- AKA palmoplantar pustular psoriasis
- Also most often seen in middle aged females
- Characterized by "sterile" pustules on palms and soles
- Pustules do not generalize and the course is chronic
- Consistent plaque psoriasis in ~24%
  - Is this a separate disease or on the spectrum of psoriasis?
- Strongly associated with smoking and thyroid disease

Smoking and PPP

- PPP is predominantly seen in middle-aged women who smoke
- Most patients presenting with PPP are smokers at the time of disease onset
- Smoking and association with PPP
  - OR 10.5 (95% CI 3.3–33.5)
  - 74-fold higher age adjusted risk of PPP among smokers
  - Cessation of smoking may lead to improvement in PPP

Pathogenesis of PPP

- PSORS1/HLA-Cw*0603 has not been found to be involved in patients with PPP
- Recently described missense mutations in IL36RN and CARD14
- Several studies have reported a significant role of IL-17 in PPP
  - One study found an 89-fold increase in IL-17A cytokine expression in PPP in contrast to IL-23 which is seen more consistently in lesions of chronic plaque psoriasis

SAPHO Syndrome

- Synovitis
- Acne
- Pustulosis
- Hyperostosis
- Osteitis
Implications on Treatment

- Cases treated with TNF agents or IL12/23 blockade have shown mixed results
- Biologics targeting IL17 may represent a more effective therapeutic option than these other agents

TNF-alpha Inhibitor Induced Psoriasis

- Majority of cases associated with:
  - Infliximab (62.5%)
  - Adalimumab (21.8%)
  - Etanercept (14.4%)
- Patients underwent treatment for an average of 14.0 months before onset

TNF-alpha Inhibitor Induced Psoriasis

Recent Systematic Review

- Paradoxical development of psoriasis while using TNF-alpha inhibitors for other disease states
  - Most common diseases:
    - Crohn’s Disease (40.7%)
    - Rheumatoid Arthritis (37.0%)
    - Ankylosing Spondylitis (13.9%)
- Psoriasis presentations are variable
  - Plaque psoriasis (44.8%)
  - Palmoplantar pustular psoriasis (36.3%)

TNF-alpha Inhibitor Induced Psoriasis

Management and Treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>N (%)</th>
<th>Infliximab</th>
<th>Adalimumab</th>
<th>Etanercept</th>
<th>Non-TNF inhibitor</th>
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</thead>
<tbody>
<tr>
<td>Biosimilar</td>
<td>22 (92.8)</td>
<td>12 (54.5)</td>
<td>10 (45.5)</td>
<td>6 (27.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
<td>TNF-alpha</td>
<td>47 (21.5)</td>
<td>7 (14.9)</td>
<td>30 (63.8)</td>
<td>4 (8.5)</td>
<td>3 (6.4)</td>
<td>3 (6.4)</td>
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<tr>
<td>Non Improvement</td>
<td>8 (20)</td>
<td>3 (15)</td>
<td>4 (20)</td>
<td>4 (20)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
<td>Poor Improvement</td>
<td>22 (47.9)</td>
<td>12 (54.5)</td>
<td>10 (45.5)</td>
<td>6 (27.3)</td>
<td>0 (0)</td>
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<td>Biologic</td>
<td>100 (100)</td>
<td>50 (50)</td>
<td>50 (50)</td>
<td>0 (0)</td>
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<tr>
<td>Switched to another TNF inhibitor</td>
<td>22 (92.8)</td>
<td>12 (54.5)</td>
<td>10 (45.5)</td>
<td>6 (27.3)</td>
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<tr>
<td>Need for additional treatment</td>
<td>14 (63.6)</td>
<td>8 (36.4)</td>
<td>6 (27.3)</td>
<td>4 (20)</td>
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Interesting Cases from UCSF

- Disequilibrium in pro-inflammatory cytokine interferon alpha levels in the setting of TNF alpha suppression is thought to contribute
- Emerging evidence suggests that the IL-23/Th17 axis plays an important role
  - In a study evaluating anti-TNF induced psoriasis in pediatric patients with CD, those who developed psoriasis were more often homozygous for three specific IL-23R polymorphisms compared to disease matched controls who did not develop psoriasis
Case #1

8 years old  14 years old  15 years old (most recent admission)

Previous Therapies

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<tr>
<th>Year</th>
<th>Therapy</th>
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<tr>
<td>2001</td>
<td>Acitretin (11/01-5/10)</td>
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<tr>
<td>2009</td>
<td>Adalimumab (12/09-2/12)</td>
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<td>2010</td>
<td>nbUVB (5-11/09)</td>
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<td>2014</td>
<td>Cyclosporine (7/08-7/09)</td>
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<tr>
<td>2015</td>
<td>Ustekinumab (2/12-9/14)</td>
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<tr>
<td>2016</td>
<td>Infliximab (9/14-6/15)</td>
</tr>
<tr>
<td>2017</td>
<td>salmon MTX (9/14-6/15)</td>
</tr>
</tbody>
</table>

History of Present Illness

Anakinra

Hospital Course

Day 1 2 3 4 5 6 7 8 9 10 11
Anakinra

Hospital Course

Day 1 2 3 4 5 6 7 8 9 10 11
Anakinra

Hospital Day 6

Hospital Day 9
Hospital Course

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Anakinra</td>
<td>High Dose Infliximab</td>
</tr>
</tbody>
</table>

Hospital Day 10

Immunophenotyping

[Image of immunophenotyping chart]

Courtesy of Michael Rosenblum, MD, PHD

10 Days After Secukinumab

[Image of patient before and after 10 days of Secukinumab]

Mutational Analysis

[Image of mutational analysis chart]

Courtesy of Wilson Liao, MD

Conclusions

This case suggests that IL-17 may be a rational therapeutic option in patients with DITRA.

Case #2

[Images of patient during admission and after discharge]
Treatment with apremilast...

6 Weeks into Treatment

Thank You!

• Haley Naik
• Wilson Liao
• John Koo
• Kelly Cordoro
• Lucy Kohn
• Mike Rosenblum