Pyoderma gangrenosum: a practical approach

Alex G Ortega-Loayza, MD
• No financial relationships exists with commercial interest
• I will discuss some off label use of medications
• 1. Introduction
• 2. The problem of PG
• 3. Pathogenesis
• 4. Current studies
1. INTRODUCTION

- Brocq’s description of PG:
  - Clinical
    - The ridge
    - The external slope
    - The internal slope
  - Histopathological
    - Necrotic inflammatory infiltrate - neutrophils
    - Depth of the infiltrate
    - Main differential diagnosis: infectious cellulitis
• Clinical
  – The ridge
  – The external slope
  – The internal slope
• Histopathological
  – Necrotic inflammatory infiltrate-neutrophils
  – Depth of the infiltrate
  – Main differential diagnosis: infectious cellulitis
Deep infiltrate
Neutrophils
Inflammatory disorder

Humoral immunity
Cellular immunity
Complement
Neutrophil function

Comorbidities
Treatment

Geometric phagedism
Pyoderma gangrenosum

1916
1930
1930s-60s
1960s-70s
1980s-90s
2. THE PROBLEM OF PG

- Epidemiology
- Cost
- Quality of life
- Association with comorbidities
- Mortality
3. PATHOGENESIS

• Multifactorial:
  – interplay of abnormal inflammatory response and genetics

• Etiology associated with autoinflammation
Neutrophil Dysfunction
- Pathergy
- Inflammatory bowel disease
- Rheumatoid arthritis (seropositive or seronegative)
- Paraproteinemia (IgA monoclonal gammopathy, Waldenstrom’s macroglobulinemia)
- Hematologic abnormalities (myelogenous leukemia, myelodysplasia, multiple myeloma)
- Solid organ malignancy (breast, gastrointestinal, genitourinary)

Inflammation
- IL-1β
- TNFα
- IL-6
- IL-8
- IL-17
- IL-23
- CXCL 1, 2, 3, 8, 16
- MMPs
- GCSF

Pathophysiology:

Genetics
- PSTPIP-1
- IL-8RA
- PRDM1
- TIMP3
- TRAF3IP2

Paget sum (PG):

Sara F. Braya, MD
Figure 2. Inflammatory mediators increased in PG, pregnancy, and both.

**PG**
- IL1β
- TNFα
- IL6
- IL8
- IL23
- CXCL 1, 2, 3, 8, 16
- MMP 2, 9
- RANTES

**Pregnancy**
- Neutrophils
- G-CSF/GM-CSF
- Th17

- Lipid peroxides
- STBMS
- DAMPS

**Unknown triggers**
- Previous history of PG
- Parainflammatory comorbidities
• Questions to be answered:
  – external triggers/sources
  – intrinsic triggers/sources
  – cytokine or group of cytokines as mediators
4. CURRENT STUDIES

• Diagnostic evaluation and management of classic ulcerative pyoderma gangrenosum: A survey of U.S. dermatologist
  
  • (Afifi, Ortega-Loayza and Shinkai on behalf of the Society of Dermatology Hospitalist; submitted)
• SDH collaborative project
• 140 surveyed from the SDH and RDS
• 51 participants
• 96% academic dermatologists
• Cases per year: range 2-35
• Aim: to report on the experience of U.S. dermatologist treating PG and address practice gaps in diagnostic evaluation and management
• **DIAGNOSTIC EVALUATION:**
  – Biopsy for H&E: always(74%)
  – Biopsy for culture: always(67%)
  – Top 3 studies ordered
    • CBC(76%)
    • Comprehensive Metabolic(73%)
    • Hepatitis(50%)
  – Additional studies frequently ordered: SPEP, ESR, CRP, ANA, ANCA, RF, cryoglobulins
TREATMENT:

1st line treatment

- Systemic corticosteroids (94%)
  - Corticosteroid > Cyclosporin = biologic = anti-neutrophilic
- Topical immunomodulatory (63%)
  - Corticosteroid (78%)
  - Calcineurin inhibitor (41%)
- Intralesional therapy (47%)
- Anti-neutrophilic agents (35%)
- Biologic or steroid sparing (27%)

Systemic CS 100%
Cyclosporin 74%
TNF alpha inh 24%

• **TREATMENT:**

• *Combination approach*
  – Topical and systemic (58%)
  • More frequently when seen >10 patients per year
  – Topical and intralesional and systemic (37%)
  – Intralesional/systemic (22%)
  – Do not use combination approach (20%)

*Al Ghazal P et al. JDDG 2015; 13: 317-24*
• **TREATMENT**

• **Wound care**
  – Refer to wound specialists: always (14%), often (32%)
  – Top 3 wound care recommendations:
    • Petroleum gauze (85%)
    • Non-stick dressings (74%)
    • Topical antimicrobials (49%)
  – Grafting: rarely (46%), never (54%)
  – Others:
    • 70% never used hyperbaric O2
    • 55% never debride
Take Home Points

• Evaluation: Consensus
  – Skin biopsies for H&E
  – Microbiological cultures
  – Others: CBC, CMP, SPEP, hepatitis panel, ESR

• Management: High volume respondents
  – Combination treatment was favored
Clinical trials as of July 2016

Study 1:  
Proof of Concept Study of Gevokizumab in the Treatment of Pyoderma Gangrenosum  
Completed  
Drug: **Gevokizumab**

Study 2:  
An Efficacy and Safety Study of Gevokizumab in Treating Active Ulcers of Pyoderma Gangrenosum  
Recruiting  
Drug: **Gevokizumab**|**Drug: Placebo**

Study 3:  
An Efficacy and Safety Study of Gevokizumab in Treating Active Ulcers of Pyoderma Gangrenosum  
Recruiting  
Drug: **Gevokizumab**|**Drug: Placebo**

Study 4:  
RA-18C3 Therapy for Subjects With Pyoderma Gangrenosum  
Recruiting  
Biological: **RA-18C3**

Study 5:  
Open Label Study for Adults With Pyoderma Gangrenosum and Inflammatory Bowel Disease  
Completed  
Has Results  
Drug: **Infliximab**

Study 6:  
Canakinumab for Pyoderma Gangrenosum  
Unknown  
Pyoderma Gangrenosum  
Drug: **Canakinumab**

Study 7:  
A 2-Year, Open-Label, Safety Extension Study of Gevokizumab in Subjects With Pyoderma Gangrenosum  
Enrolling by invitation  
No Results Available  
Drug: **Gevokizumab**

Study 8:  
A single arm study to assess a potential effect of Anti-IL-17(Secukinumab) in the treatment of pyoderma gangrenosum  
Recruiting  
Drug: **Secukinumab**

Inhibitors of interleukin-1

<table>
<thead>
<tr>
<th>Anakinra</th>
<th>Rilonacept</th>
<th>Canakinumab</th>
<th>Gevokizumab</th>
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</thead>
<tbody>
<tr>
<td><strong>IL-1Ra</strong></td>
<td><strong>IL-1R/IL-1RAcP-Fc</strong></td>
<td><strong>Anti-IL-1β antibody</strong></td>
<td><strong>Anti-IL-1β antibody</strong></td>
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<tr>
<td><strong>Structure</strong></td>
<td><strong>Fc fusion protein</strong></td>
<td><strong>IgG1 mAb</strong></td>
<td><strong>IgG2 mAb</strong></td>
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<tr>
<td><strong>Binding to IL-1α</strong></td>
<td><strong>Yes</strong></td>
<td><strong>No</strong></td>
<td><strong>No</strong></td>
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<tr>
<td><strong>Affinity to IL-1β</strong></td>
<td><strong>None</strong></td>
<td><strong>23 pmol</strong></td>
<td><strong>300 fmol</strong></td>
</tr>
<tr>
<td><strong>Half life</strong></td>
<td><strong>5 hours</strong></td>
<td><strong>26 days</strong></td>
<td><strong>22 days</strong></td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td><strong>100 mg daily</strong></td>
<td><strong>150 mg single dose</strong></td>
<td>–</td>
</tr>
<tr>
<td><strong>Approved</strong></td>
<td><strong>RA, CAPS</strong></td>
<td><strong>CAPS (only USA)</strong></td>
<td>–</td>
</tr>
<tr>
<td><strong>Off label use</strong></td>
<td><strong>sJIA, AOSD, CPPD</strong></td>
<td><strong>CAPS, gout, sJIA</strong></td>
<td>–</td>
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<tr>
<td></td>
<td><strong>Gout, CPPD, HACD</strong></td>
<td><strong>AOSD, Schnitzler syndrome</strong></td>
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<td><strong>Schnitzler syndrome</strong></td>
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<tr>
<td><strong>In testing</strong></td>
<td>–</td>
<td>–</td>
<td><strong>CVD, diabetes</strong></td>
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<tr>
<td><strong>Refs</strong></td>
<td>143</td>
<td>144,145</td>
<td>147</td>
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Nature Reviews 2016; 12:14-24-
RESULTS OF AN OPEN-LABEL, PROOF OF CONCEPT STUDY OF GEVKIZUMAB IN THE TREATMENT OF THE ACUTE, INFLAMMATORY PHASE OF PYODERMA GANGRENOSUM

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**Gevokizumab Treatment Reduced Target Ulcer Size & Total Ulcer Size**

Data from Subject 2000 was suppressed. The subject had an increase of 3900% in target ulcer size by Day 84.

**Gevokizumab Treatment Improved Pain Scores**

Data from Subject 2000 was suppressed. The subject had an increase of 600% in total ulcer size by Day 84.
Canakinumab in gangrenosum

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CONCLUSIONS

• Pathogenesis
  • It is multifactorial
    – Inflammatory mediators
    – Genetics
  • Autoinflammatory phenomenon
• Evaluation and Management
  • Experience vs Consensus
Thank You