Complex Psoriasis Cases from Virginia

ABBY S. VAN VOORHEES, MD
OCTOBER 26, 2019

Conflict of Interest

- I have served as a consultant to the following companies: Derm Tech, WebMD, Novartis, Lilly, UCB
- I have participated in clinical trials for the following companies: Celgene, Lilly, AbbVie
Preferred assessment instrument: Body Surface Area (BSA)

<table>
<thead>
<tr>
<th>Time Post Initiation</th>
<th>Target</th>
<th>Acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Months</td>
<td>BSA ≤ 1%</td>
<td>BSA ≤ 3% or 75% Improvement</td>
</tr>
<tr>
<td>Every 6 Months</td>
<td>BSA ≤ 1%</td>
<td></td>
</tr>
</tbody>
</table>


Current Treatment Paradigm

Topical Therapy → Failure → Biologic Agents
- Adalimumab
- Brodalumab
- Certolizumab
- Etanercept
- Guselkumab
- Infliximab
-Ixekizumab
-Risankizumab
-Secukinumab
-Tildrakizumab
-Ustekinumab

Phototherapy
- UVB
- PUVA

Traditional Systemic Agents
- Acitretin
- Apremilast
- Cyclosporine
-Methotrexate
- Other immunosuppressants

Personal Opinion: Craig Leonardi
Comparison of PASI 75 Scores After 12 Weeks of Therapy


Comparison of PASI 90 Scores After 12 Weeks of Therapy

Outline of cases

- Pustular psoriasis
- The place for methotrexate
- How to handle those with Tuberculosis

Case 1

- 34-year-old female who initially presented with a flare of pustular eruption at week 37. She had previously been treated with oral prednisone without improvement. Her clinical exam was remarkable for diffuse erythema studded with pustules of the trunk and extremities. She was diagnosed with pustular psoriasis of pregnancy (PPP), however before treatment was initiated she delivered her child and the rash spontaneously resolved. Ten months postpartum while still breastfeeding she developed a pustular eruption limited to the left axilla and adjacent flank. A pregnancy test was negative. Topical therapies including tacrolimus 0.1% ointment and triamcinolone acetonide 0.1% cream were not beneficial.
Pustular psoriasis

• **Severe multisystem disease**
  ○ Sudden widespread eruption of pustules
  ○ Associated with fever, chills,
  ○ +/− preceding plaque psoriasis
  ○ Can cause cardiorespiratory failure esp in elderly
  ○ No medications approved in US, but in Japan the following are approved:
    ▶ Secukinumab, Ixekizumab, Brodalumab, Guselkumab

Criteria for diagnosis of pustular psoriasis

<table>
<thead>
<tr>
<th>Japanese</th>
<th>Europeans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic symptoms</td>
<td>Sterile pustules on non-acral skin +/- plaque psoriasis</td>
</tr>
<tr>
<td>Diffuse erythema + sterile pustules forming lakes of pus</td>
<td>Can be relapsing or persistent</td>
</tr>
<tr>
<td>Neutrophilic subcorneal pustules= Kogoj’s spongiform pustules</td>
<td></td>
</tr>
<tr>
<td>Repeated recurrences</td>
<td></td>
</tr>
</tbody>
</table>

Types of pustular psoriasis

- Acute GPP (von Zumbusch)-most common, >50%
- Pustular psoriasis of pregnancy (Impetigo herpetiformis)
- Infantile/juvenile pustular psoriasis
- ? Acute generalized exanthematous pustulosis (AGEP)
- ? Sneddon Wilkinson

Triggers

- Internal triggers: infection, pregnancy
- External triggers: steroid withdrawal, initiation of ustekinumab, other medications
Histology of skin

Pathogenesis

- Identified mutations leading to dysregulation of pro-inflammatory pathways
  - Lack of IL36R inhibition associated with loss of function mutation in IL36RN
  - CARD4 mutation
  - AP1S3

Pustular psoriasis of pregnancy (PPP)

**Features**
- Annular lesions with sterile pustules
- Onset in skin folds (axilla and breasts) and spreads outward
- Systemic symptoms: fever, chills, malaise, nausea, joint pain
- Onset third trimester
- Associated with poor neonatal outcome
- Rapid resolution with delivery, recurrence possible with subsequent pregnancy
- Leukocytosis with dominance of neutrophils, elevated ESR, reduced albumin

**Histology**
- Same as GPP

Treatments for pustular psoriasis

- Acitretin**
- Cyclosporin*
- Methotrexate**
- Biologics with fast onset of action
  - Infliximab

* Category C, ** Category X

## Pregnancy risk

<table>
<thead>
<tr>
<th>Category B</th>
<th>Unknown</th>
</tr>
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<tbody>
<tr>
<td>- Etanercept</td>
<td></td>
</tr>
<tr>
<td>- Infliximab</td>
<td></td>
</tr>
<tr>
<td>- Adalimumab</td>
<td></td>
</tr>
<tr>
<td>- Certolizumab*</td>
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</tr>
<tr>
<td>- Ustekinumab</td>
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</tr>
<tr>
<td>- Secukinumab</td>
<td></td>
</tr>
<tr>
<td>- Ixekizumab</td>
<td></td>
</tr>
<tr>
<td>- Brodalumab</td>
<td></td>
</tr>
<tr>
<td>- Guselkumab</td>
<td></td>
</tr>
<tr>
<td>- Taldrakizumab</td>
<td></td>
</tr>
<tr>
<td>- Risankizumab</td>
<td></td>
</tr>
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</table>

## Treatments for pustular psoriasis of pregnancy

- **Biologics**
  - **Category B**
    - Can be considered in first half of pregnancy due to active transplacental transport after week 22
    - Certolizumab may limit transport during pregnancy due to structure
      - Pegylated anti-TNF inhibitor
Certolizumab

Clowse ME, et al. J Rheumatol 2018

<table>
<thead>
<tr>
<th>Event</th>
<th>All (n=538)</th>
<th>Rheumatic diseases (n=305)</th>
<th>CD (n=200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live birth</td>
<td>459/538</td>
<td>256/305</td>
<td>203/200</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>17/538</td>
<td>9/305</td>
<td>8/200</td>
</tr>
<tr>
<td>Induced abortion</td>
<td>17/538</td>
<td>14/305</td>
<td>3/200</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>5/538</td>
<td>3/305</td>
<td>2/200</td>
</tr>
</tbody>
</table>

What about when nursing?

Our current patient
Mechanism of lactation

Binding of Fc portion of IgG to mammary epithelial cells needed for IgG transfer to be released into the alveolar lumen for transmission into breast milk.

Since Certolizumab lacks Fc portion leading to a lack of active transfer & transmission into breast milk.

Digestion by gastric acid leading to protein degradation and lack of absorption through gastric mucosa also limit systemic absorption.

Our patient

- Therapy was initiated on certolizumab with excellent response and clearing of pustules and erythema. Infant tolerated well.

Case 2

43 year old African American male presented in clinic with onset of psoriasis x 5 yrs. He has health insurance but no prescription coverage. He is miserably pruritic, and therefore willing to pay out of pocket for his treatment. He denies joint symptoms. He is unable to afford copays associated with phototherapy. His PE remarkable for widespread plaque psoriasis; BSA 15% scattered on his truck and extremities. He is borderline overweight and has been trying hard to lose additional weight. He has no other medical problems, drinks rarely and is fearful of injections.
**Methotrexate**

- Competitive inhibitor of dihydrofolate reductase leading to reduction in folate cofactors needed for nucleic acid synthesis.
- Increased amount of adenosine which is anti-inflammatory
- Reduction of proliferation of lymphoid cells leading to immunosuppression

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**How effective is MTX?**

- SKIN
- JOINTS
MTX in Psoriasis: The METOP Study

- Investigator initiated DBPC trial
- 120 study subjects enrolled
  - 91: MTX
  - 29: PBO → MTX
- Subcutaneous injection
- Initial dose MTX: 17.5 mg
- Dose escalation to 22.5 mg @ Week 8 for < PASI-50
- Primary endpoint: Week 16
- PBO-crossover @ Week 16


MTX in Psoriasis: Results from the METOP Study

ITT-NRI Analysis

MTX → MTX: n = 91
PBO → MTX: n = 29

Comparison of PASI 75 Scores After 12 Weeks of Therapy\textsuperscript{1-8}


Simplified EULAR and GRAPPA Treatment Algorithms for Predominant Peripheral Psoriatic Arthritis\textsuperscript{1-3}

## Simplified EULAR and GRAPPA Treatment Algorithms for Predominant Enthesal Psoriatic Arthritis\(^1\-^3\)

<table>
<thead>
<tr>
<th><strong>EULAR</strong></th>
<th><strong>bDMARD</strong></th>
<th><strong>Switches</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs ± local glucocorticoid injections as indicated</td>
<td>Usually TNF inhibitor</td>
<td>TNF inhibitor</td>
</tr>
<tr>
<td></td>
<td>IL-12/23 inhibitor</td>
<td>IL-12/23 inhibitor</td>
</tr>
<tr>
<td></td>
<td>IL-17 inhibitor</td>
<td>IL-17 inhibitor</td>
</tr>
<tr>
<td></td>
<td>PDE4 inhibitor</td>
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<td>TNF inhibitor</td>
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Both groups recommend the use of bDMARDs without prior use of a csDMARD


## Simplified EULAR and GRAPPA Treatment Algorithms for Predominant Axial Psoriatic Arthritis\(^1\-^3\)

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<td></td>
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Both groups recommend the use of bDMARDs without prior use of a csDMARD

### Toxicity

- **Common:** nausea, vomiting, fatigue, stomatitis, anorexia
- **Immunosuppression:** increased risk of infections including TB reactivation & hepatitis
- **More severe:** hepatotoxicity, myelosuppression, pneumonitis
  - Bone marrow suppression-seen most commonly in elderly, low folate levels, renal impairment, moderate alcohol intake
  - Hepatic toxicity-seen most commonly in obesity, diabetes, hyperlipidemia

### RISKS FOR USE OF MTX

**Table II.** Risk factors for hepatotoxicity from methotrexate

- History of or current greater than moderate alcohol consumption (methotrexate toxicity is associated with a history of total lifetime alcohol intake before methotrexate therapy; the exact amount of alcohol that leads to risk is unknown and differs from person to person)
- Persistent abnormal liver chemistry study findings
- History of liver disease including chronic hepatitis B or C
- Family history of inheritable liver disease
- Diabetes mellitus
- Obesity
- History of significant exposure to hepatotoxic drugs or chemicals
- Hyperlipidemia

Adapted with permission from Kalb et al. ⁴
### Methotrexate liver biopsy recommendations

**GOC 2010**

<table>
<thead>
<tr>
<th>NO RISK FACTORS</th>
<th>+ RISK FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider liver bx after cumulative dose 3.5-4 gm MTX OR consider following LFT’s if wnl</td>
<td>• Baseline liver biopsy (can be delayed until efficacy established)</td>
</tr>
<tr>
<td></td>
<td>• Repeat liver biopsy after 1-1.5 gm MTX</td>
</tr>
</tbody>
</table>

### Alternative liver testing options

- **Serologic studies**
  - Fib4-free, based on lab values (liver enzymes, age and platelet count)
  - Fibrotest/fibrosure
  - Fibrometer
  - Hepascore
- **Radiographic studies**
  - Vibration-controlled transient elastography
### Cost issues

- **Dosing equivalence of pill formulation vs. liquid formulation**
  - 2.5 mg pill = 0.1 cc liquid formulation (25 mg/ml)

### Balancing the +/-

<table>
<thead>
<tr>
<th>Advantages of MTX</th>
<th>Disadvantages of MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral formulation</td>
<td>Slow onset of action</td>
</tr>
<tr>
<td>Inexpensive</td>
<td>Moderate efficacy</td>
</tr>
<tr>
<td>No associated weight gain</td>
<td></td>
</tr>
</tbody>
</table>

Our patient

Started initially on MTX 15 mg weekly with reduction of BSA to 5%. Dose of MTX was then increased to 20 mg weekly with further improvement in BSA to 1%. LFT’s have remained stable at baseline levels.

Case 3

- 57 year old SubAsian male with long-standing history of psoriasis whose disease has been worsening over past 3 months. He was initially treated with topical steroids followed by apremilast without benefit. In July 2019 a QG test was performed and found to be positive; other labs were wnl. His SH is remarkable for the fact that he is originally from India and travels frequently back to India to visit family. Upon presentation he noted severe pruritus and skin pain, but denied joint symptoms. His exam was remarkable for widespread erythematous plaques of his chest, abdomen, back, right and left arms and legs and buttocks. BSA 42%.
What comes next?

A. UVB PHOTOThERAPY
B. REPEAT APREMILAST
C. METHOTREXATE
D. BIOLOGIC AGENT
E. ACITRETIN

Chest X-ray findings

LINEAR DISCOID ATELECTASIS IN LEFT MIDLUNG WHICH WAS STABLE SINCE 10/20/17 BUT WITHOUT EVIDENCE FOR TB
PATIENT WAS STARTED ON INH AND HAS TAKEN IT FOR 2 MONTHS.

Next steps?

Therapeutic choices

- Etanercept
- Infliximab
- Adalimumab
- Certolizumab
- Guselkumab
- Tildrakizumab
- Risankizumab
- Secukinumab
- Ixekizumab
- Brodalumab

- Methotrexate
- Acitretin
- Cyclosporin
Therapeutic choices

Our patient

- Patient was started on ixekizumab concurrent with his INH therapy for his latent TB. BSA has been reduced to 1%.
Thank you

vanwooas@evms.edu