Non-Biologic Therapies for Psoriasis

- Keratolytics
  - Salicylic Acid, Urea
- Corticosteroids
- Vit D Analogs
  - Calcipotriene
- Calcineurin inhibitors
  - Tacrolimus
- Topical Retinoids
  - Tazarotene
- Tars
  - Goeckerman Technique
  - Ingram Technique
- Anthralins
  - Dihydroxyanthralin

- UV Light
  - UVA +/- psoralen, UVB, narrow band UVB
  - 311nm laser device
- Methotrexate
- Cyclosporine
- Acitretin
- Emerging Therapies

Topical Therapies

- Most commonly prescribed form of treatment
- Frequently used in combination with other topicals and with systemic therapies
- Several options
  - Over the counter (OTC)
  - Prescription
- Typically applied once or twice a day, each
- Vehicle matters
  - effect, side effect
  - creams, ointments, lotions, solutions, foams, gels, shampoos, and baths
Keratolytics

• Help to debride scale and allow other medications to penetrate better.
• Urea 20%-80% cream and gel
• Sal Acid: 3-5% in cold cream or hydrophilic ointments
  – Rare: salicylate toxicity with tinnitus, confusion, refractory hypoglycemia, esp in Pts with diabetes or renal disease.

Corticosteroids

• Suprapotent (Class I) Corticosteroids for body and extremities
• Low potency for body folds and face

• Pick one in each class and remember it!
  – Class 1: clobetasol, halobetasol
  – Class 6: desonide, hydrocortisone

  • Consideration of vehicle
  • Rotational or alternating therapy to minimize AEs

Vitamin D Analog

• Calcipotriene 0.005%
  – Vitamin D₃ analog that regulates KC differentiation
  – Available as cream, ointment or solution
  – Ointment form works best
  – Should be applied 2x/day to be effective
  – May be irritating to unaffected skin
  – Often used in combination/rotation with a topical steroid
  – Also comes branded in combination with betamethasone dipropionate

Calcineurin inhibitors

• Tacrolimus 0.03%, 0.1% ointment; Pimecrolimus 1% cream
  – Inhibits T-cell activation by inhibiting the synthesis and release of cytokines (IL-2) from T-cells.
  – Ointment vehicle works best
  – Better on thin skin areas (ie face, groin)
  – Should be applied 2x/day to be effective
  – May cause local irritation
  – May be in rotation with a topical steroid

Retinoids

• Tazarotene 0.05%, 0.1% cream and gel
  – Vitamin A derivative that binds retinoic acid receptors (RAR β and RAR γ)
  – Modulates KC differentiation and proliferation, and suppresses inflammation
  – Local irritation is treatment limiting

Phototherapy
**Phototherapy**

- Light unit directing ultraviolet light in specific wavelengths to affected areas
- Proposed mechanisms:
  - Alterations in cytokine expression with suppression of Th1/Th17 inflammatory axis
  - Apoptosis of several cell types in the skin
    - Activated T cells in epidermis and dermis, Keratinocytes, and to a lesser degree Langerhans cells
  - Suppression of Langerhans cell function
- Present day utilization: nbUVB >>> PUVA


**Non-Biologic Systemic Medications for Psoriasis**

**Methotrexate**

- Exact MOA of MTX for inflammatory disease is complex.
- MTX transported into variety of cells
- Intracellular glutamation
- MTXGlun inhibition of key enzymes in the folate pathway
- Inhibition and accumulation of AICAR and ATIC nucleotides → increased adenosine into circulation.
- Extracellular adenosine → increased cAMP
- cAMP inhibits production of pro-inflammatory cytokines (TNF-α, IFN-γ and IL-1β)


- Dose: 10-25 mg weekly + folic acid 1mg daily
- PASI 75 achieved in 35-42%
- AEs: GI upset, oral ulcers, hair shedding, fatigue >>> marrow suppression, hepatic fibrosis, pulmonary fibrosis
- Pregnancy category: X


Liver Biopsy?

- CSA 5 mg/kg/day yielded PASI 75 response in 50 to 97% of patients
- CSA 2.5 mg/kg/day yielded PASI 75 response in 28 to 85%
- Remission could be maintained at CSA dose of at least 3 mg/kg/day. More than 50% of patients treated with CSA may have an increase in serum creatinin value >30% of baseline if treatment is prolonged for 2 years.
- CSA 2.5 mg/kg/day effective in 89% of patients with palmoplantar pustulosis.
- CSA 3 to 5 mg/kg/day yielded a significant improvement in >50% of patients with erythrodermic psoriasis

Cyclosporine

- CSA 5 mg/kg/day yielded PASI 75 response in 50 to 97% of patients
- CSA 2.5 mg/kg/day yielded PASI 75 response in 28 to 85%
- Remission could be maintained at CSA dose of at least 3 mg/kg/day. More than 50% of patients treated with CSA may have an increase in serum creatinin value >30% of baseline if treatment is prolonged for 2 years.
- CSA 2.5 mg/kg/day effective in 89% of patients with palmoplantar pustulosis.
- CSA 3 to 5 mg/kg/day yielded a significant improvement in >50% of patients with erythrodermic psoriasis

Acitretin

- Dose: 10-50mg daily
- Oral retinoid that slows KC proliferation and stimulates differentiation
- Interferes with intracellular metabolism of natural retinoids. Competes with retinoic acid for CRABP binding and activates retinoic acid nuclear receptors
- Teratogen. Not given to women of child bearing age.
- Etretinate formed when acitretin used with ethanol.
  - Detected in 100% patients with an average weekly consumption of >200g alcohol (15 pints of beer)

PsA Treatment

- Education and counseling
- Weight loss
- Physical therapy and conditioning
- Bracing, adaptive aids
- Intra-articular/enthesial injections
- Addressing treatment of co-morbidities
  - CV (hyperlipidemia, obesity, hypertension), depression, fibromyalgia, sleep pathology, etc.
- Pharmacotherapy
PsA: Choosing Therapy

- Considerations in choice of therapy:
  - Determining which patients will progress and should be treated aggressively
  - Evidence of efficacy in arthritis, enthesitis, dactylitis, spondylitis and psoriasis (including nails)
  - Function and Quality-of-life considerations
  - Safety factors
  - Method of administration
  - Economic realities

GRAPPA: Treatment Guidelines for PsA on the Basis of Severity

- Mild
  - NSAID
  - TOPICALS
  - PHYSIO

- Moderate to severe
  - DMARDS
  - BILOGICS
  - NSAID INJECTION

Reassess response to therapy and toxicity if patient fails to demonstrate an acceptable clinical improvement over an appropriate period

EULAR PsA Management Recomendations: Use of Synthetic DMARDs in PsA

- Patients with active PsA and a potentially poor prognosis should be started on DMARDs
  - According to the EULAR guidelines for management of PsA, methotrexate (MTX) is the first choice synthetic DMARD for PsA
  - Synthetic DMARDs do not appear to be effective for the treatment of enthesitis and axial disease
  - None of the synthetic DMARDs have demonstrated efficacy for limiting structural damage in PsA

Steroid Injections

- Sacroiliac and peri-sacroiliac steroid injections appear beneficial in small randomized trials.
- Steroid injection of inflamed peripheral joints may be beneficial

Traditional PsA Therapy

- Nonsteroidal anti-inflammatory drugs
- Corticosteroids
- DMARDs
  - Sulfasalazine
  - Methotrexate
  - Leflunomide
  - Cyclosporine
  - Antimalarials

DMARDs in PsA

<table>
<thead>
<tr>
<th>Drug</th>
<th>N RCTs / N Patients</th>
<th>N Other Studies</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>3 / 93</td>
<td>7</td>
<td>Efficacy (minimal) on joints and skin X-rays no data</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>7 / 666</td>
<td>2</td>
<td>Efficacy on joints</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>1 / 190</td>
<td>3</td>
<td>Efficacy on joints</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>3 / 206</td>
<td>6</td>
<td>Efficacy on joints and skin X-rays no data</td>
</tr>
</tbody>
</table>

Effectiveness of MTX in PsA in a Randomized, Placebo-Controlled Trial (MIPA)

**DBRCT, 221 pts, Active oligo- or polyarthrits, 6 Months**

<table>
<thead>
<tr>
<th>Global Index after 6 Mo</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PsARC</td>
<td>1.77 (0.9, 3.23)</td>
<td>.06</td>
</tr>
<tr>
<td>ACR20</td>
<td>2.00 (0.86, 4.22)</td>
<td>.23</td>
</tr>
<tr>
<td>DAS28</td>
<td>1.70 (0.90, 2.17)</td>
<td>.10</td>
</tr>
</tbody>
</table>

- No evidence of a significant effect of MTX on PsARC, ACR20, DAS28, joint counts, ESR, CRP, pain and HAQ scores after 6 months treatment
- The only significant benefits of MTX treatment of PsA were in physician and patient global assessments (Ps=0.03 and Ps=0.001, respectively) and skin scores (Ps=0.02).


Effectiveness of MTX in PsA in Open-Label RESPOND Trial

ACR responses at week 16 in patients with PsA treated with infliximab (IFX) plus MTX (n=57) or MTX alone (n=58) in an open-label trial. All patients were MTX naive and were not taking DMARDs prior to treatment.

**Limitations of Conventional Systemic Therapies for PSO/PSA**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Adverse Event</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Miscarriage, Immunosuppression, Drug interactions (Leukopenia, Thrombocytopenia), Birth defects, Renal elimination, Malignant lymphoma, bone marrow failure, cirrhosis, pain, GI intolerance</td>
<td>Liver disease, active infection, pregnancy, lactation impaired renal function, active infections</td>
</tr>
<tr>
<td>Cyclosporine (Tezolimus)</td>
<td>Nephrotoxicity, Hypertension, Malignancy, Drug interactions (Cyclosporine P450), Hypermethemoglobinemia</td>
<td>Acute infections, active malignancies, uncontrolled hypertension, impaired renal function</td>
</tr>
</tbody>
</table>

Limitations of Conventional Therapy

<table>
<thead>
<tr>
<th>Agent</th>
<th>Adverse Event</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine (1-3 mg/kg/d)</td>
<td>Bone marrow suppression, infection, GI hypoplasia, n, and intravascular, pancreatitis, hepatoxicity, hepatic veno-occlusive disease, lymphoma</td>
<td>Hypersensitivity, Pregnancy (D), active infection, careful with concurrent allopurinol</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Hypertension, Diabetes, Osteoporosis, Osteonecrosis, iatrogenic Cushing's Disease, Cutaneous atrophy, &quot;Buffalo Hump&quot;, TB, Infection</td>
<td>Hypersensitivity, systemic fungal infection, caution if CHF, failure, DM, hTN, TB, osteoporosis, impaired liver function</td>
</tr>
<tr>
<td>Anti-metals</td>
<td>Retinopathy, hemolytic, bone marrow suppression (+ G6PD), blue-black pigmentation of skin, e.g. bleaching of hair, psoriasis flare, ichthyoid dermatitis, erythroderma, cicatricial T AN, AM, T digoxin, kaolin and Mg triphosphate, absorption AM</td>
<td>Hypersensitivity, Retinal disease, 1st pregnancy, porphyria</td>
</tr>
</tbody>
</table>

Limitations of Conventional Systemic Therapies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfasalazine</td>
<td>Marginally effective in reducing arthritis symptoms</td>
<td>Blood dyscrasias, Gastrointestinal reactions, hepatotoxicity, hypersensitivity reactions</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>Improves clinical and radiologic outcomes</td>
<td>Diarrhea, increased transaminase levels</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>Ablation of mild inflammation with mild joint involvement</td>
<td>Allergy, gastrointestinal bleeding, gastric or duodenal ulceration or bleed, peripheral edema, hypertension, salt retention, elevation of blood pressure, hepatic toxicity, renal dysfunction, worsening or flare of porphyria</td>
</tr>
</tbody>
</table>

Emerging Non-Biologic Therapies in Psoriasis and PsA

Apremilast (PDE4 inhibitor)
Tofacitinib (JAK inhibitor)

Intracellular Signaling Pathways

Apremilast (PDE4i) Modulates the Production of Pro-inflammatory and Anti-inflammatory Mediators

Pro-inflammatory Mediators
(i.e., TNF-α, IL-17, IL-23, IFN-γ)

Anti-inflammatory Mediators
(i.e., IL-10, TGF-β)

Apremilast Inhibits Cells, Cytokines, Chemokines Implicated in Psoriasis

PALACE 1: Apremilast in PsA

- Apremilast is an oral phosphodiesterase 4 (PDE4) inhibitor
- RDBPC trial stratified for DMARD use, N=489, 1:1:1 randomization
- Major adverse events diarrhea and nausea, resolve over time

ACR20 Response over 52 Weeks: PALACE 1, 2, 3 Apremilast 30 mg BID

Patients Receiving Apremilast from Baseline Data as Observed


Kavanaugh A, et al. ACR Fall Meeting 2014 [oral presentation].

Kavanaugh A, et al. EULAR 2013 [oral presentation].

Cutolo M. SIR 2013 [oral presentation].

Cutolo M. ACR 2013 [oral presentation].

Apremilast Effects on Enthesitis and Dactylitis

Data Pooled from PALACE 1–3 Week 24

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mean Change</th>
<th>95% CI</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>MASIS (0-13)</td>
<td>-0.9</td>
<td>-1.0 to -0.7</td>
<td>P = 0.001</td>
</tr>
<tr>
<td>Dactylitis count</td>
<td>1.0</td>
<td>0.9 to 1.1</td>
<td>P = 0.001</td>
</tr>
</tbody>
</table>

*P<.02 vs placebo; †P<.01 vs placebo.

Gladman DD, et al. ACR. 2013, San Diego, #816

Efficacy of Apremilast in Psoriasis Skin Lesions in PsA

PASI 75 at Week 16

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Subjects achieving PASI-75, %</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>APR 10 mg BID</td>
<td>11.2</td>
<td>P&lt;.01 vs placebo</td>
</tr>
<tr>
<td>APR 20 mg BID</td>
<td>28.8</td>
<td>P&lt;.001 vs placebo</td>
</tr>
<tr>
<td>APR 30 mg BID</td>
<td>40.9</td>
<td>P&lt;.001 vs placebo</td>
</tr>
</tbody>
</table>

*P<.01 vs placebo.

Oral administration; Phase 2b

Apremilast in Psoriasis

ESTEEM 1: PASI-75, PASI-50, and sPGA Response at Week 16

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients Achieving Response (%)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Apremilast 30 mg BID</td>
<td>60.6</td>
<td>P&lt;.001 vs placebo</td>
</tr>
</tbody>
</table>

*P<.001 (FAS, LOCF); §Patients with baseline ScPGA scores ≥3. **Patients with nail psoriasis at baseline.

Mean Change from Baseline in Pruritus VAS at Week 16

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients (%</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>17.5</td>
<td></td>
</tr>
<tr>
<td>Apremilast 30 mg BID</td>
<td>28.7</td>
<td>P&lt;.0001</td>
</tr>
</tbody>
</table>

Mean Change from Baseline in DLQI at Week 32

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients (%)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>30.0</td>
<td></td>
</tr>
<tr>
<td>Apremilast 30 mg BID</td>
<td>38.2</td>
<td>P&lt;.001</td>
</tr>
</tbody>
</table>

Apremilast: Safety

- GI Intolerance (nausea and diarrhea) and headache are most significant AEs
- PI (PSA) notes weight loss and depression in warnings section
- PI does not recommend use of strong cytochrome p450 enzyme inducers because loss of efficacy may occur
Efficacy of Tofacitinib in Psoriasis

Coprimary Endpoints:
Patients Achieving PASI 75 and PGA Responses at Week 12

PASI 75

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PASI 75 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tofacitinib 5 mg BID (n = 329)</td>
<td>39.5</td>
</tr>
<tr>
<td>Tofacitinib 10 mg BID (n = 330)</td>
<td>47.1</td>
</tr>
<tr>
<td>Etanercept 50 mg BIW (n = 335)</td>
<td>63.6</td>
</tr>
<tr>
<td>PBO (n = 107)</td>
<td>68.2</td>
</tr>
</tbody>
</table>

PGA Response

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PGA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tofacitinib 5 mg BID (n = 329)</td>
<td>75.0</td>
</tr>
<tr>
<td>Tofacitinib 10 mg BID (n = 330)</td>
<td>54.8</td>
</tr>
<tr>
<td>Etanercept 50 mg BIW (n = 335)</td>
<td>66.2</td>
</tr>
<tr>
<td>PBO (n = 107)</td>
<td>66.3</td>
</tr>
</tbody>
</table>

PGA = Physician’s Global Assessment.

TEAEs

Incidence of Treatment Emergent Adverse Events (TEAEs)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PASI 75 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tofacitinib 5 mg BID</td>
<td>20.0</td>
</tr>
<tr>
<td>Tofacitinib 10 mg BID</td>
<td>25.0</td>
</tr>
<tr>
<td>Etanercept 50 mg BIW</td>
<td>28.0</td>
</tr>
<tr>
<td>PBO</td>
<td>15.0</td>
</tr>
</tbody>
</table>

Patients with any TEAE, n (%): 329/329 (100), 329/329 (100), 330/330 (100), 107/107 (100)
Patients with serious TEAEs, n (%): 7 (2.1), 5 (1.5), 7 (2.1), 2 (1.9)
Decrease in TEAE, n (%): 7 (2.1), 5 (1.5), 7 (2.1), 2 (1.9)

- The most frequent adverse events were infections (most commonly nasopharyngitis and upper respiratory tract infection).
- Hypertension and decreases in HDL-c and LDL-c and dyslipidemia were more common in tofacitinib recipients, as was an increase in creatinine phosphokinase.
-Injection site reactions were most frequent among etanercept recipients.


Baricitinib:
A Second Oral JAK Inhibitor

- %PASI 75 at week 12 of once daily dosing:
  8 mg 43%, 10 mg 54%, PBO 17% P<.05

Menter et al. AAD. 2014;P7941.

Treating to Target in PsA

Minimal Disease Activity Criteria (MDA) (GRAPPA)

- A patient is classified as in MDA when they meet 5 of 7 of the following criteria:
  - tender joint count ≤ 1
  - swollen joint count ≤ 1
  - PASI ≤ 1 or BSA ≤ 3
  - patient pain VAS ≤ 15
  - patient global activity VAS ≤ 20
  - HAQ ≤ 0.5
  - tender entheseal points ≤ 1

The TICOPA Study

**Aim**
- Does treat to target using MDA criteria improve outcome in psoriatic arthritis?

**Primary Outcome**
- ACR20 at 48 weeks

**Sample Size Calculation**
- 50% ACR20 response with standard care
- 70% ACR20 response with tight control
- Sample size = 186, alpha = 0.05, beta = 0.8

**Registered Trial EudraCT No 2007-004757-28**

**Primary Outcome – Complete Case Analysis**

**PASI Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI75</td>
<td>2.02</td>
<td>1.51</td>
<td>2.57</td>
<td>.02</td>
</tr>
<tr>
<td>PASI90</td>
<td>5.00</td>
<td>5.11</td>
<td>7.39</td>
<td>.0004</td>
</tr>
<tr>
<td>PASI40</td>
<td>0.34</td>
<td>0.34</td>
<td>0.34</td>
<td>.0002</td>
</tr>
</tbody>
</table>

**Prescribed Therapy at 48 Weeks**

**TICOPA Trial Design**

**INTENSIVE MANAGEMENT GROUP**
- MTX and SSZ
- Escalating to 1g bd at 4-8 wks, then to 40mg/kg/day max

**STANDARD THERAPY GROUP**
- MTX
- Start at 15mg/wk escalating to 25mg/wk at 6 weeks

**TICOPA (n=206)**

**Primary Outcome**
- Complete Case Analysis
  - ACR20: Tight Control vs Standard Care
  - PASI75: 72% vs 52% (P = .0015)
  - PASI90: 52% vs 33% (P = .0004)
  - PASI40: 42% vs 25% (P = .0002)

**N=172 N=170 N=172**
Serious Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Tight Control</th>
<th>Standard Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SAE</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>SAE related to drug</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Blood/lymph system</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>GI</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Immune system</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Infection/infestation</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Injury/poisoning</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>MSK and CTD</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nervous system</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Renal/urinary</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Reproductive/breast</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory and thoracic</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>


Conclusions

- Treatment recommendations
  - Establishing diagnosis is critical
  - Determine severity of clinical domains involved and assess impact on function and QoL
  - Sensitivity to patient’s concerns about safety and therapy choices
- Management team
  - Patient
  - Physical, occupational therapy
  - Dermatology
  - Rheumatology
  - Counseling
  - Surgery

Questions & Answers