Psoriasis: A Therapeutic Update

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Alta Dermatology/LECOM
Disclosures

• I have no relevant financial or nonfinancial relationships to disclose.
Objectives

• Brief review of the pathogenesis of psoriasis
• Discuss traditional treatment options for psoriasis
• Introduce emerging therapeutic options for psoriasis
• Appreciate a “whole-person” approach to psoriasis
Psoriasis

• Chronic inflammatory disease
• Systemic inflammatory state
  • Obesity, diabetes mellitus, cardiovascular disease, dyslipidemia, etc...
  • Up to 30% of patients with psoriatic arthritis
  • Up to 60% with clinical depression
• Earlier onset associated with more severe disease
• Affects 2% of the population
Pathogenesis of Psoriasis
Triggering factors
Genetic Predisposition
Chronic T cell activation
Board Review

Triggering factors

- Infection
- Trauma
- Stress
- Drugs
  - ACE inhibitors
  - Beta blockers
  - Lithium
  - Rapid steroid withdrawal
Genetic Predisposition

- HLA-Cw6 & B17 $\rightarrow$ early onset disease
- HLA-B27 $\rightarrow$ arthritis
- HLA-B13 & B17 $\rightarrow$ guttate
Abnormal chronic T cell activation:

- Stressed keratinocytes
  - TNFα, IL-1, IL-6
- Dendritic cells activated
  - Present “antigen”
- Naïve T cells differentiate
- TH1, TH17, TH22 migrate to psoriatic dermis from the lymph and blood
- Psoriatic plaque develops
Abnormal chronic T cell activation:

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- TH1, TH17, TH22 migrate to psoriatic dermis from the lymph and blood
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Abnormal chronic T cell activation:

- TH1 cells release TNF\(\alpha\) amplifying inflammatory cascade
  - IL-12 stimulates TH1
  - TH17 cells secrete TNF\(\alpha\), IL-17 and IL-22
  - IL-23 and IL-17 stimulates TH17
Abnormal chronic T cell activation:

- TH1 cells release TNFα amplifying inflammatory cascade
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### Board Review

Abnormal chronic T cell activation

- IL-12 stimulates TH1
- IL-23 stimulates TH17

**Recall:**
- IL-12 and IL-23 have common subunit p40 (target of ustekinumab)
Abnormal chronic T cell activation:

- TH22 cells secrete IL-22, inducing further recruitment of T cells
- IL-22 levels correlate with disease severity
Traditional Therapies

To find health should be the object of the doctor. Anyone can find disease.
—A.T. Still
Topical Agents

• Majority of patients with mild to moderate disease can be treated with topical agents only
• Generally provide both high efficacy and safety
• Can also be used as an adjunct for resistant lesions or extensive disease
Topical Agents

• Topical Corticosteroids
• Vitamin D analogues
• Topical retinoids
• Calcineurin inhibitors
• Keratolytics
• Anthralin
• Coal Tar
• Salt-water baths
Topical Agents

- **Topical Corticosteroids**
- Vitamin D analogues
- Topical retinoids
- Calcineurin inhibitors
- Keratolytics
- Anthralin
- Coal Tar
- Salt-water baths

- Anti-inflammatory and antiproliferative
- 80% of patients experience clearance with high-potency topical corticosteroids
- Maximum improvement usually achieved within 2 weeks
- Decrease to alternate day dosing for prolonged courses
- Side effects: Tachyphylaxis and rebound can occur rapidly
Topical Agents

• Topical Corticosteroids
• **Vitamin D analogues**
• Topical retinoids
• Calcineurin inhibitors
• Keratolytics
• Anthralin
• Coal Tar
• Salt-water baths

• Antiproliferative
• ~60% reduction of PASI after 8 weeks
• Combination with a high-potency topical corticosteroid → greater efficacy and a more rapid onset of action than either agent alone
• Not to use >100 grams weekly
• Not for use on face or body folds
• Side effects: burning, irritation, hypercalcemia, hypercalciurea
Topical Agents

• Topical Corticosteroids
• Vitamin D analogues
• **Topical retinoids**
• Calcineurin inhibitors
• Keratolytics
• Anthralin
• Coal Tar
• Salt-water baths

• Antiproliferative
• 50% improvement noted in half of patients using tazarotene gel twice daily after 6 weeks
• Up to 10-20% BSA
• Side effect: irritating
Topical Agents

- Topical Corticosteroids
- Vitamin D analogues
- Topical retinoids
- **Calcineurin inhibitors**
  - Keratolytics
  - Anthralin
  - Coal Tar
  - Salt-water baths

The diagram illustrates the mechanism of action of Calcineurin Inhibitors, showing how they bind FK506-binding protein and inhibit Calcineurin, which is involved in T-cell receptor activation and cytokine (e.g., IL-4) production. The diagram highlights the clinical efficacy of these agents, with 65% of patients achieving almost clear results at 8 weeks.
Topical Agents

- Topical Corticosteroids
- Vitamin D analogues
- Topical retinoids
- **Calcineurin inhibitors**
- Keratolytics
- Anthralin
- Coal Tar
- Salt-water baths

- Facial and flexural areas
- 65% almost clear at 8 weeks
- Side effects: burning and itching that improves with usage
- Controversial black box warning
Topical Agents

- Topical Corticosteroids
- Vitamin D analogues
- Topical retinoids
- Calcineurin inhibitors

Keratolytics
- Anthralin
- Coal Tar
- Salt-water baths

- Salicylic acid 5-10%
- Useful for thick scaling lesions of scalp or other localized areas
- Use 2-3 times weekly
Topical Agents

- Topical Corticosteroids
- Vitamin D analogues
- Topical retinoids
- Calcineurin inhibitors
- Keratolytics

**Anthralin**
- Coal Tar
- Salt-water baths

- Antiproliferative
- Side effects: odor, staining, irritation
Topical Agents

- Topical Corticosteroids
- Vitamin D analogues
- Topical retinoids
- Calcineurin inhibitors
- Keratolytics
- Anthralin

- Coal Tar
- Salt-water baths

- Anti-inflammatory, anti-proliferative

- Side effects: odor, staining, contact dermatitis
Topical Agents

- Topical Corticosteroids
- Vitamin D analogues
- Topical retinoids
- Calcineurin inhibitors
- Keratolytics
- Anthralin
- Coal Tar
- Salt-water baths
## Systemic Agents

### Table 1
Selected patient considerations in systemic psoriasis therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent or severity of psoriasis</td>
<td>Typically &gt;10% BSA, or involved areas significantly impede quality of life</td>
</tr>
<tr>
<td>Presence of psoriatic arthritis</td>
<td>Consider systemic, disease-modifying therapy regardless of level of skin involvement</td>
</tr>
<tr>
<td>Woman of childbearing potential</td>
<td>Not a good candidate for most oral psoriasis medications</td>
</tr>
<tr>
<td>Man attempting to conceive a child</td>
<td>Not a good candidate for methotrexate</td>
</tr>
<tr>
<td>Chronic or binge alcohol user</td>
<td>Avoid concomitant therapies with significant risk of hepatotoxicity</td>
</tr>
<tr>
<td>History of hepatitis</td>
<td>Avoid therapies with significant risk of hepatotoxicity</td>
</tr>
<tr>
<td>History of hematologic malignancy</td>
<td>Use immunosuppressants with caution</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>Avoid immunosuppressants</td>
</tr>
<tr>
<td>Smoker</td>
<td>Counsel on quitting</td>
</tr>
</tbody>
</table>
Systemic Agents

<table>
<thead>
<tr>
<th>Frequent</th>
<th>Less Frequent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comprehensive metabolic panel</td>
<td>Magnesium, phosphate</td>
</tr>
<tr>
<td>Complete blood count</td>
<td>β-human chorionic gonadotropin</td>
</tr>
<tr>
<td></td>
<td>HIV serology</td>
</tr>
<tr>
<td></td>
<td>Lipid panel</td>
</tr>
<tr>
<td></td>
<td>Hepatitis B serology</td>
</tr>
<tr>
<td></td>
<td>Hepatitis C serology</td>
</tr>
<tr>
<td></td>
<td>Interferon-gamma releasing assay for</td>
</tr>
<tr>
<td></td>
<td>the detection of latent tuberculosis or purified</td>
</tr>
<tr>
<td></td>
<td>protein derivative tuberculin</td>
</tr>
</tbody>
</table>

Kelly III et al
Systemic Agents

• Phototherapy
• Methotrexate
• Cyclosporine
• Systemic retinoids
Systemic Agents

- **Phototherapy**
- Methotrexate
- Cyclosporine
- Systemic retinoids

  - Decreased cellular proliferation, apoptosis of T cells, suppression of Langerhans cells
  - Narrow band UVB (311-313 nm) optimal
    - Remission rate up to 55% at 1 year
  - Excimer laser (308 nm) for limited, localized plaques
  - Side effects: erythema/blistering, photoaging, theoretical risk of photocarcinogenesis
Systemic Agents

- Phototherapy
- **Methotrexate**
- Cyclosporine
- Systemic retinoids

- Oldest systemic therapy for psoriasis (>40 years)
- Increases endogenous adenosine levels (potent anti-inflammatory)
- 40% achieve PASI 75 at week 16
- Monitoring for rare, severe side effects (liver, bone marrow, lung)
  - Psoriasis is an independent risk factor for liver disease
Systemic Agents

- Phototherapy
- Methotrexate
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Systemic Agents

• Phototherapy
• Methotrexate
• **Cyclosporine**
• Systemic retinoids

• Calcineurin inhibitor: inhibits T cell activation
• Used as bridge therapy, for severe flares or refractory disease
• Up to 88% achieve PASI 75
• Use for up to 1 year
• Monitoring
  • Hypertension, nephrotoxicity, ↓Mg  
  ↑uric acid, ↑K, gingival hyperplasia
Systemic Agents

- Phototherapy
- Methotrexate
- Cyclosporine
- **Systemic retinoids**

- Anti-proliferative effects on keratinocytes
- Not immunosuppressive
- Up to 41% achieve PASI 75
- Poor tolerability
- Effective for pustular or erythrodermic psoriasis
- Side effects: abnormal LFTs, hyperlipidemia, pseudotumor cerebri, etc...
Systemic Agents

Phosphodiesterase 4 inhibitor (apremilast):
• Downregulates TNFα, IL-2, IL-12, IL-23
• FDA approved for psoriasis and psoriatic arthritis
• Side effects:
  • Diarrhea, nausea, headache, URI, weight loss, depression
  • Starter pack dosing and resolution of GI symptoms in first month
• 33% achieve PASI 75 at week 16
• No need for blood monitoring
## Systemic Agents

<table>
<thead>
<tr>
<th>Target</th>
<th>Biologic Agent(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNFα</td>
<td>Etanercept, Infliximab, Adalimumab</td>
</tr>
<tr>
<td>p40 subunit of IL-12/23</td>
<td>Ustekinumab</td>
</tr>
<tr>
<td>IL-17</td>
<td>Secukinumab, Brodalumab, Ixekizumab</td>
</tr>
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## Systemic Agents

<table>
<thead>
<tr>
<th>Target</th>
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<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNFα</td>
<td>Etanercept</td>
<td>68-80% achieve PASI 75</td>
<td>Concern for infection</td>
</tr>
<tr>
<td></td>
<td>Infliximab</td>
<td>20-57% achieve PASI 90</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adalimumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Up to 70% achieve PASI 75</td>
<td>Concern for infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28% achieve PASI 100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ustekinumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Up to 87% achieve PASI 75</td>
<td>Concerns for invasive candidiasis and Crohn’s exacerbations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>54% achieved PASI 90</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>44% achieve PASI 100</td>
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</table>
New and Emerging Therapies

My father was a progressive farmer, and was always ready to lay aside an old plough if he could replace it with one better constructed for its work. All through life, I have ever been ready to buy a better plough.

- A.T. Still
New and Emerging Therapies

JAK inhibitors (Tofacitinib and Ruxolitinib):

• FDA approved for rheumatoid arthritis
• Impedes a wide array of inflammatory cytokines, including IL-12 and IL-23
• Phase III trials (topical and systemic formulations)
• Side effects:
  • Risk of infection, theoretical increased risk of malignancy (interferes with anti-tumor responses), cytopenias, lipid abnormalities
• Up to 63% achieve PASI 75 at week 12
Other Emerging Therapies

• IL-23 inhibitors (Guzelkumab, Tildrakizumab)
  • Up to 81% achieve PASI 75 in phase II studies

• Adenosine A3 receptor antagonists
  • Decrease proinflammatory cytokines, including TNFα

• Oxidized phospholipids
  • Inhibits secretion of inflammatory markers, such as TNFα, IL-12 and IL-23

• Fumaric acid derivatives
  • Approved in Europe, not the US
  • Efficacy on par with methotrexate; requires lab monitoring
  • Shifts inflammatory infiltrate towards Th2 and away from Th1 and Th17

• Sphingosine 1-phosphate receptor-1 modulators
  • Inhibits migration of T lymphocytes into circulation
  • Concern with cardiac conduction abnormalities

• And others....
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- And others....
A “Whole Person” Approach

We look at the body in health as meaning perfection and harmony, not in one part, but in the whole.
—A.T. Still
Obesity and Psoriasis

- Obesity = chronic inflammatory state
- Obese patients have higher risk of severe disease and reduced response to therapy
  - Adipocytes produce TNFα, IL-6, leptin
  - Obese patients have higher levels of IL-17 and IL-23 compared to lean patients
- Inflammatory markers decrease with weight loss
Effect of Weight Loss in Psoriasis Management

Results:

• Median PASI reduction of 48% in intervention group (vs 25%)
• PASI 50 achieved by 49% of intervention group (vs 34%)
Find a Registered Dietitian Nutritionist

The Academy of Nutrition and Dietetics’ Find a Registered Dietitian Nutritionist online referral service allows you to search a national database of Academy members for the exclusive purpose of finding a qualified registered dietitian nutritionist or food and nutrition practitioner who is right for you (no solicitations, please).

Active category Academy members can sign up for Find an RDN at www.eatright.org/myAcademy

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Or Search by expertise
• Unique patients with unique needs
  • Osteopathic manipulation?
  • Yoga?
  • Massage?
  • Mindfulness?
  • Prayer?
  • Diet?

• Team approach!
The usage of complementary therapies by dermatological patients: a systematic review

E. Ernst

Department of Complementary Medicine, School of Postgraduate Medicine and Health Sciences, University of Exeter, U.K.

Accepted for publication: 30 Dec 1999

- Complementary medicine is more popular than ever before
- Lifetime prevalence ranged from 35-69%
- Only 40% of complementary therapy use is discussed with physicians
- Consider discussing complementary medicine openly with patients
Integrative dermatology for psoriasis: facts and controversies

Valori Treloar, MD, CNS

Integrative Dermatology, 1172 Beacon St, Ste 402, Newton, MA 02461
Integrative Dermatology

• Quit smoking
• Limit alcohol intake
• Sleep 8 uninterrupted hours nightly
• Learn and practice daily a relaxing activity
• Eat a nutrient dense diet (consider working with a nutritionist)
• Exercise 5-7 days a week (ex. brisk walk 20 minutes daily)
Thank you

I find in man a miniature universe.
—A. T. Still


