Therapeutic challenges in the diagnosis and management of psoriasis

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Disclosure of relevant relationships with industry - Posted on AAD web site

- Investigator and/or consultant for
  - Abbvie, Amgen, Celgene, Dermira, Janssen, Leo, Merck, Pfizer, Taro
- Dermatology Safety Monitoring Board
  - ApoPharma, Eli Lilly
- No promotional speaking

Objectives

- Safety and efficacy of therapy
- Guidelines for treatment
- Influence of comorbidities
- Challenges
- Emerging therapies
Conclusions

- Psoriasis can be a devastating disease both physically and emotionally
- There is very effective treatment
  - Topical versus systemic therapy
- Effective therapy is a control not a cure

Managed care conclusions

- Eliminate phototherapy co-payments
- No restrictions or prior authorizations for phototherapy or conventional systemic therapy (methotrexate, cyclosporin, acitretin)
- Biologic prior authorization policy
  - One prior systemic therapy failure?
Psoriasis morbidity

- Skin symptoms
  - Itching, Burning, Open areas of skin
- Obesity
- Depression
- Psoriatic arthritis
- Cardiovascular risks
  - Will psoriasis therapy decrease these risks?
Do we underestimate the impact of psoriasis on patients’ lives?
Disability associated with psoriasis vs other major medical diseases (N=317)

SF-36 Scores

Physical

Mental

Psoriasis
HTN
Post-MI
CHF
Diabetes
Depression

Rapp SR, el J Amer Acad Dermatol 1999;41:401-407

Classifying and measuring psoriasis

- Mild, moderate, severe?
- BSA (Body surface area)
  - 3%, 5%, 10%, 30%?
- Studies use PASI scores
  - Psoriasis Area Severity Index
  - Gold standard is PASI 75%
- Treatable topically
- Needs systemic approach
Localized psoriasis therapy

- Topical steroid therapy with or without a vitamin D analogue
  - Calcipotriene (Dovonex®)
  - Calcitriol (Vectical®)
  - Both available generically
- Potency of topical steroid depends on area involved
No chance for topical therapy

Previous therapy

- Clindox Spray 0.05%
- Clindox Shampoo 0.05%
- Clindox Propionate 0.05%
- Alopixen Cream 0.06%
- Hydrocortisone oint 2.5%
- Desoximetasone oint 1.25%
- Monistatase Emolge oint 1%
- Clindox Propionate oint 0.05
- Betamethasone Dipropionate cream 0.05%
- Hydrocortisone Valerate cream 2%
- Monistatase Foroste Topical solution 1%
- Tazorac cream 0.05%
- Desoximetasone Cream 0.25%
- Elcon Ointment 1%
- Vancos cream 1%
- Betamethasone Dipropionate 0.05
Psoriasis therapy

Treatment Toolbox

Traditional Systemic Agents
- Methotrexate
- Cyclosporine
- Acitretin
- Apremilast

Phototherapy
- UVB
- PUVA

Biologic Agents
- Adalimumab
- Etanercept
- Infliximab
- Ustekinumab

Narrow band UVB phototherapy
UVB Phototherapy

- NB-UVB (narrow band ultraviolet B)
- NB-UVB is now the gold standard for phototherapy
- Requires proper equipment, 2-3X per week visits
- Minor acute and chronic side effects
UVB Phototherapy

Two main issues

Access
- Not available in many areas

Co-payments
- Most plans charge for each session
- $50 per session = $600/month

Annual cost to achieve PASI 75 response
Methotrexate

- Once per week (~15 mg) oral therapy
- Gold standard therapy for rheumatoid and psoriatic arthritis
- PASI 75 about 40%
- Possible bone marrow and hepatic toxicity
Methotrexate

- Lab monitoring requirements
- Alcohol avoidance
- Relatively inexpensive
- Can be administered subcutaneously
  - Has advantages (safety, efficacy)
  - New commercial product (Otrexup®)
Cyclosporin

- Daily dosing (3-5 mg/kg)
- Quick response
- Hypertension and renal toxicity
- FDA label restricted to one year of therapy
  - Long term use limited
Acitretin

- Oral retinoid (Vitamin A) derivative
- Not cytotoxic or immunosuppressive
- Better when combined with phototherapy or systemic therapy
- Excellent maintenance drug
- Typical retinoid dose related side effects

Biologic therapy for psoriasis

- TNF blocking agents
  - Adalimumab (Humira®)
  - Etanercept (Enbrel®)
  - Infliximab (Remicade®)
- IL 12/23 blocking agents
  - Ustekinumab (Stelara®)
How does insurance pay for these medicines?

- Pharmacy benefit
  - Etanercept, adalimumab, ustekinumab

- Medical benefit
  - Physician administered SQ or IV
  - Physician buys drug, bills J code
  - Infusion center / MD office
    - Infliximab, ustekinumab

Etanercept (Enbrel®) therapy

<table>
<thead>
<tr>
<th>Time</th>
<th>PASI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>18.7</td>
</tr>
<tr>
<td>12 Weeks</td>
<td>7.6</td>
</tr>
<tr>
<td>24 Weeks</td>
<td>2.5</td>
</tr>
</tbody>
</table>
Etanercept (Enbrel®) therapy

- Self injected SQ 1-2X/week
- Approved for psoriasis, psoriatic arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis
- FDA approved for double dose first 12 weeks for psoriasis, then 50 mg once per week
Adalimumab (Humira®) therapy

Baseline | Week 12 | Week 24
--- | --- | ---

- PASI Score 15.4 (PASI 75 Response)
- PASI Score 3.3
- PASI Score 1.5 (PASI 90 Response)

Adalimumab (Humira®)

- Self injected once every other week
- Approved for psoriasis, psoriatic arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease
- Very effective for skin lesions
- #1 biologic for psoriasis
Ustekinumab (Stelara®) 45 mg (after 2 doses)

Baseline

Week 12

PASI Score = 43.9

PASI Score = 0.4

Ustekinumab (Stelara®)

- Dose 45 mg <100 kg / 90 mg >100 kg
- Administered at week 0, 4 and then every 12 weeks
- Interval between injections can vary significantly
<table>
<thead>
<tr>
<th>Administration</th>
<th>Adalimumab (Humira®)</th>
<th>Etanercept (Enbrel®)</th>
<th>Infliximab (Remicade®)</th>
<th>Ustekinumab (Stelara®)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SQ every other week</td>
<td>SQ 1X/week</td>
<td>2 hr IV infusion every 8 weeks after induction</td>
<td>SQ every 12 weeks</td>
</tr>
<tr>
<td>Type</td>
<td>Human monoclonal antibody TNFα</td>
<td>Receptor fusion protein TNFα</td>
<td>Chimeric monoclonal antibody TNFα</td>
<td>Human monoclonal antibody IL-12/23</td>
</tr>
<tr>
<td>Efficacy (PASI 75) at 12 wks, 1 year</td>
<td>~70% ~60%</td>
<td>~50% ~45%</td>
<td>~80% ~60%</td>
<td>~70% ~60-70%</td>
</tr>
<tr>
<td>Safety</td>
<td>Rare but serious side effects</td>
<td>Rare but serious side effects</td>
<td>Rare but serious side effects</td>
<td>Rare but serious side effects (?less infections)</td>
</tr>
<tr>
<td>FDA status</td>
<td>Psoriasis Psor Arth</td>
<td>Psoriasis Psor Arth</td>
<td>Psoriasis Psor Arth</td>
<td>Psoriasis Psor Arth</td>
</tr>
<tr>
<td>Pediatric use for other indications</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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</table>
Psoriasis comorbidity
Semin Cut Med Surg 29:10, 2010

- Cardiovascular
- Metabolic syndrome
- Hypertension
- Obesity
- Type II diabetes
- Arthritis
Psoriasis and cardiovascular disease

- Is the association between psoriasis and CV disease a causal relationship (systemic inflammation driving CV risk)?
- Will systemic therapy for psoriasis with MTX / biologic therapy reduce CV risk?

Cardiovascular mortality and psoriasis

- The first study to examine CV death while adjusting for CV risk factors
  - Eur Heart J. 2009 Dec 27. Epub ahead of print PMID: 20037179
- Severe psoriasis was an independent risk factor for CV mortality (HR 1.57; 95% CI 1.26, 1.96)
  - When adjusted for age, sex, smoking, diabetes, hypertension, and hyperlipidemia
Six meta-analyses link psoriasis and cardiovascular disease

Cardiovascular event rates in psoriasis patients

- Retrospective longitudinal cohort study in Denmark over 3 years 2400 patients
- Biologic agents / MTX associated with less events (death, MI, stroke) compared to cyclosporin, retinoids, phototherapy, topicals

Cardiovascular mortality and psoriasis

- Retrospective cohort study - Kaiser Permanente health plan 8845 patients
- Does therapy change MI risk?

<table>
<thead>
<tr>
<th>Pair</th>
<th>MI rate ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral agents/phototherapy vs topical agents</td>
<td>0.57 (0.41–0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TNF inhibitors vs oral agents/phototherapy</td>
<td>0.79 (0.49–1.28)</td>
<td>0.34</td>
</tr>
<tr>
<td>TNF inhibitors vs topical agents</td>
<td>0.45 (0.30–0.68)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Surrogate markers of CV inflammation

- Gold standard - decrease in mortality
- FDG-PET scan
  - 18-fluorodeoxy glucose
- Statin therapy shows decrease in vascular inflammation via FDG-PET
- Will psoriasis therapy?

Uptake of $^{18}$F-FDG in carotid artery

Bissonnette et al Circ Cardiovasc Imaging 6:83; 2013
How much of the cardiovascular risk is directly attributable to psoriasis?
- Certainly a portion

Significant risks are associated with severe skin disease
- Usually defined by having received systemic therapy for psoriasis

Does treatment with conventional systemic or biologic therapy improve cardiovascular risk in psoriasis?
- Current evidence is suggestive

Patients with severe psoriasis need intensive management of cardiovascular risk factors and appropriate psoriasis therapy
Next generation agents

- Interleukin 17 blocking agents
- Phosphodiesterase 4 inhibitor
  - Apremilast (Otezla®)
- JAK inhibitor – Tofacitinib (Xeljanz®)
- p19 antibodies (IL-23 blocker)
  - Tildrakizumab, Guselkumab

Newer agents IL-17 pathway

- IL 17A/F antagonists NEJM 366:1251, 2012
  - Brodalumab (Amgen) Blocks receptor
    - Phase II NEJM 366:1181, 2012
  - Ixekinumab (Lilly)
    - Phase II NEJM 366:1190, 2012
  - Secukinumab (Novartis)

- PASI 75 in 80% range
- Cautious optimism
Secukinumab Phase III
PASI 75 at 12 weeks

Newer oral agents

- Phosphodiesterase (PDE) 4 inhibitor
  - Apremilast (Otezla®)
  - Recently approved for psoriasis
- Janus kinase (JAK) inhibitors
  - Tofacitinib (Xeljanz®)
  - Approved for rheumatoid arthritis
Apremilast (Otezla®)

- Psoriasis data presented at AAD meeting in Denver 2014
  - Phase III – 844 patients
- PASI 75 – 33% (placebo - 5%)
  - Small oral molecule
  - No significant side effects (minor GI issues)
  - Cost ~75% of biologics

Tofacitinib (Xeljanz®)

- Approved in US for rheumatoid arthritis at 5 mg BID dose
  - EAME did not approve
- Minor adverse events
- ? degree of immunosuppression
Tofacitinib Non-inferiority study
PASI 75 at 12 weeks

Presented at AAD in Denver March, 2014
Psoriatic arthritis (PsA)

- Does biologic therapy prevent joint destruction?
  - Yes but in a small % of patients
  - Who are these patients?

- Therapy
  - Methotrexate, anti-TNF agents
  - Three newer options

TNF antagonists for psoriatic arthritis
ACR 20/50/70 responses at week 24

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Adalimumab 40 mg eow (N = 151)</th>
<th>Etanercept 25 mg biw (N = 101)</th>
<th>Infliximab 5 mg/kg (N = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>57</td>
<td>50</td>
<td>54</td>
</tr>
<tr>
<td>ACR50</td>
<td>39</td>
<td>37</td>
<td>41</td>
</tr>
<tr>
<td>ACR70</td>
<td>23</td>
<td>9</td>
<td>27</td>
</tr>
</tbody>
</table>
Ustekinumab for psoriatic arthritis
ACR 20/50/70 responses at week 24

Apremilast for psoriatic arthritis
ACR 20/50/70 responses at week 24

doi: 10.1016/S0140-6736(13)60594-2. PMID: 23769296

Therapy access

- Prior authorization for biologic therapy
- Significant geographic variation
- BC of California
  - Failure of phototherapy and 2 systemic agents / 30% body surface area
- Phototherapy
  - Co-payment issues
Clinical criteria

- Fail to respond to conventional therapy
- Side effects with conventional therapy
- Unstable disease
- Significant co-morbidities
- Psoriatic arthritis
  - Possibly prevent joint destruction

Annual cost AWP Oct 2014

- Etanercept Step down $52,900
- Adalimumab 40mg QOW $45,400
- Ustekinumab 45 mg $35,400
- Ustekinumab 90 mg $70,800
- Apremilast 30 mg BID $27,000
- Tofacitinab 5 mg BID $34,000
Insurance payors / PBM’s

- Want information regarding cost efficacy
- Systemic treatment options are burgeoning
- Head-to-head efficacy trials have started
- Study assumptions over 1 year
  ◦ PASI data over 12 weeks

PASI 75 at 12 weeks
Head to head trials
Br J Dermatol 170:274, 2014

- Superiority of adalimumab and infliximab over methotrexate (MTX)
- Superiority of ustekinumab over etanercept
- Superiority of secukinumab over etanercept
- Non-significant superiority of cyclosporine vs MTX
- Non inferiority of tofacitinib vs etanercept

Conclusions

- Psoriasis can be a devastating disease both physically and emotionally
- There is very effective treatment
  - Topical versus systemic therapy
- Effective therapy is a control not a cure
Managed care conclusions

- Eliminate phototherapy co-payments
- No restrictions or prior authorizations for phototherapy or conventional systemic therapy (methotrexate, cyclosporin, acitretin)
- Biologic prior authorization policy
  - One prior systemic therapy failure?

Managed care conclusions

- Biologic therapy has revolutionized psoriasis treatment
- Major challenge - Who will benefit most from the more expensive biologic therapy?
  - Cardiovascular disease
  - Arthritis
  - Quality of life measures
THANK YOU

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