Update on the burden and treatment of moderate to severe psoriasis

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Disclosure statement

• I have been an investigator and/or consultant for Amgen, Abbvie, Jansen, Merck (DSMB), Pfizer, Lilly, Celgene, Coherus (DSMB), and Novartis
• This presentation is the sole work of Dr. Gelfand
Learning Objectives

1. Review prevalence and disease burden of the psoriasis population
2. Discuss the use of biologics and management strategies
3. Evaluate the best strategies for managing side effects and comorbidities to improve quality of life
4. Discuss combination treatments for psoriasis
5. Assess efficacy and safety of current and emerging treatments for psoriasis

Psoriasis Epidemiology

- **Prevalence**
  - Affects 2-3% of adult population (> 7 million in US)
  - Caucasians: 2.5%
  - African Americans: 1.3% (more likely to have moderate to severe disease)

- **Disease severity**
  - 15% have moderate disease (3-10% BSA)
  - 5% have severe disease (>10% BSA)

Psoriasis natural history

- Chronic disease with typical onset in 20’s to 30’s
- Genetic susceptibility
  - 40% have + family history
  - *HLA-Cw6* most commonly implicated
  - >40 genes implicated
- Any part of skin can be affected including face, scalp, nails, genitals
- Majority of patients with more severe psoriasis remain poorly controlled for decades

Psoriasis Vulgaris – Clinical Features

[Images of skin lesions]
Differential Diagnosis of Psoriasis

- Autoimmune diseases
  - SCLE, Dermatomyositis
- Cancer
  - Mycosis fungoides, SCC, BCC
- Infection
  - Tinea, Scabies, Syphilis
- Other skin dz
  - Eczema, PRP, Lichen Planus
- Drug reaction

Guttate Psoriasis – Clinical Features

- Small papules of psoriasis (5mm)
- Eruptive
- Often associate with URI/Strep
- Remission/flare is common
Pustular Psoriasis – Clinical Features

- Eruptive pustules
- Fever
- Arthralgia
- Requires urgent evaluation and treatment
Erythrodermic Psoriasis – Clinical Features

- Impaired epidermal barrier function
- High output CHF
- Infection
- Electrolyte disturbances

Nail Psoriasis

- Onycholysis
- Nail pitting
- Subungual debris
Genital Psoriasis

Inverse Psoriasis
Psoriasis Impact on Quality of Life Compared to Other Major Morbidities

QOL outcome was SF-36 physical and mental health domains

<table>
<thead>
<tr>
<th></th>
<th>Mental Functioning</th>
<th>Physical Functioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy adults</td>
<td>53.43</td>
<td>Healthy adults</td>
</tr>
<tr>
<td>Diabetes type 2</td>
<td>51.90</td>
<td>Depression</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>51.67</td>
<td>Arthritis</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>50.43</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Arthritis</td>
<td>48.81</td>
<td>Lung disease</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>45.89</td>
<td>Diabetes type 2</td>
</tr>
<tr>
<td>Lung disease</td>
<td>44.47</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Depression</td>
<td>34.84</td>
<td>Congestive heart failure</td>
</tr>
</tbody>
</table>


QOL and Psoriasis – Descriptive Studies

- “We almost never talk about it, so I feel alone with my disease and all that it entails”
- “The only thing you think of is scratching, bathing, and putting on ointment…24 hours a day”
- On remission: “I suddenly found myself singing for joy. It was like getting out of prison. You were free. There was nothing holding you back anymore.”

“Only psoriasis could have taken a very average boy…and made him into a prolific, adaptable, ruthless-enough writer”

*At war with my skin* in Self Consciousness by John Updike

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**Joseph Stalin**

- Stalin was successfully treated with “lysates” by Dr. Kazakow
- Stalin closed the State Institute of Skin and Venereal Diseases in favor of a new institute for Dr. Kazakow to study lysate therapy
- Stalin’s psoriasis relapsed
- Dr. Kazakow was tried and executed

Psoriasis Pathophysiology

- Localized and systemic inflammation
  - Defects in T regs
  - Upregulation of Th1 and Th-17 cells, APCs and cytokines
  - Associated with increased CRP and other markers of inflammation
- Epidermal Hyper-proliferation
  - Clinically appreciated as scaling, cracking
  - Associated with elevated uric acid, and oxidative stress
- Angiogenesis
  - Clinically appreciated as “Auspitz” sign
  - Associated with increased circulating VEG-F
- Genes
  - >40 susceptibility loci

Inflammatory markers associated with psoriasis improve CV risk prediction in healthy women

Psoriasis and cardiometabolic disease: Mechanistic insights

Metabolic and CV gene expression > cycle and inflammatory disease categories in lesional vs non lesional psoriasis biopsies

KC-Tie2 psoriasis skin specific inflammation mouse model demonstrates development of aortic inflammation and thrombosis


Psoriasis is more than skin deep: results from advanced FDG-PET/CT Imaging

- Psoriasis is associated with increased vascular inflammation independent of traditional risk factors and equivalent to 10 years of aging
- Subclinical inflammation in liver and joints
Clinical Implications: Comprehensive care for psoriasis patients

Old Paradigm: “Just a skin disease”

New paradigm: “A systemic disease”

Mediating factors
- Pathophysiology
  - Th1/17 inflammation (atherosclerosis, thrombosis, lipid metabolism)
  - Epidermal proliferation (uric acid, oxidative stress)
  - Angiogenesis (endothelial dysfunction)
- Treatment
  - Increase CV risk (e.g. cyclosporine, acitretin)?
  - Decrease CV risk (e.g. methotrexate)?
- Psychosocial impact
  - Depression, alcohol and smoking, lower socioeconomic status

Psoriasis and co-morbidities paradigm

Environmental risk factors
- Smoking
- Obesity

Genes and loci associated with psoriasis, diabetes and CV diseases
- PSORS2/3/4
- CDKAL1
- ApoE4
- TNFAIP3

Mediating factors
- Pathophysiology
- Treatment
- Psychosocial impact


CV: cardiovascular.
Well established comorbidities of psoriasis

- Heart Attack, Stroke, CV death
- Metabolic syndrome (obesity, insulin resistance, cholesterol abnormalities, hypertension)
- Diabetes
- Psoriatic arthritis
- Mood Disorders (anxiety, depression, suicide)
- Crohn’s Disease
- T cell lymphoma (rare)

Emerging co-morbidities

- Sleep apnea
- Nonalcoholic steatohepatitis (NASH)
- Chronic obstructive pulmonary disease (COPD)
- Adverse infectious disease outcomes
- Chronic and end stage renal disease
- Peptic ulcer disease

References:


Risk of Cardiometabolic Disease in Patients with More Severe Psoriasis

Clinical Significance:
1. Increased risk of MI, stroke, cardiovascular death, diabetes, chronic kidney disease and
2. 5 years of life lost
3. 10 year risk of major CV event attributable to psoriasis = 6%
4. Risk of cardiovascular disease in patients with severe psoriasis similar to risk conferred by diabetes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adj. RR Mild</th>
<th>Adj. RR Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI¹</td>
<td>1.05</td>
<td>1.5</td>
</tr>
<tr>
<td>Stroke²</td>
<td>1.06</td>
<td>1.4</td>
</tr>
<tr>
<td>CV Death³</td>
<td>Not done</td>
<td>1.6</td>
</tr>
<tr>
<td>MACE⁴</td>
<td>Not done</td>
<td>1.5</td>
</tr>
<tr>
<td>Diabetes⁵</td>
<td>1.11</td>
<td>1.5</td>
</tr>
<tr>
<td>Chronic Kidney Dz⁶</td>
<td>0.99 (NS)</td>
<td>1.9</td>
</tr>
</tbody>
</table>


Comparison of cardiometabolic outcomes: Psoriasis vs. RA

Baseline prevalence of MI, cerebro and peripheral vascular disease in iHOPE (N= 9000)


New Clinical Care Recommendations: Educate and Screen for CV risk factors

A/JC Editor’s Consensus: Psoriasis and Coronary Artery Disease

Vincent E. Friedewald, MD, Jennifer C. Cather, MD, Joel M. Gelfand, MD, MSCE, Kenneth B. Gordon, MD, Gary H. Gibbons, MD, Scott M. Grundy, MD, PhD, Michael T. Jarratt, MD, James G. Krueger, MD, Paul M. Ridker, MD, Neil Stone, MD, and William C. Roberts, MD

National Psoriasis Foundation clinical consensus on psoriasis comorbidities and recommendations for screening

Alexa B. Kimball, MD, MPH, Dafna Gladman, MD, Joel M. Gelfand, MD, MSCE, Kenneth Gordon, MD, Elizabeth J. Horn, PhD, MD, Neil J. Korman, MD, PhD, Gretchen Korver, MD, PhD, Gerald G. Krueger, MD, Bruce E. Strober, MD, PhD, and Mark G. Lebwohl, MD, for the National Psoriasis Foundation

CV risk factors are under screened and under managed in psoriasis patients

- CDC US population data indicates poor screening rates for hypertension
  - Severe psoriasis dermatology: 4%
  - Non psoriasis/non dermatology: 61%
- Danish psoriasis patients on biologics were less likely to receive pharmacotherapy for established CV risk factors

Should psoriasis be aggressively treated to lower the risk of CV disease?

TNF inhibitors and methotrexate are cardioprotective in RA meta-analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TNF (RR)</th>
<th>MTX (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV all</td>
<td>0.70</td>
<td>0.72</td>
</tr>
<tr>
<td>MI</td>
<td>0.59</td>
<td>0.81</td>
</tr>
<tr>
<td>CHF</td>
<td>0.75 (NS)</td>
<td>0.8</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.52</td>
<td>0.78 (NS)</td>
</tr>
<tr>
<td>MACE</td>
<td>0.30</td>
<td>0.38 (NS)</td>
</tr>
</tbody>
</table>


Randomized Placebo Controlled Trials evaluating impact of anti-inflammatory treatment on CV risk

- **Vascular Inflammation in Psoriasis Trial (VIP) and VIP-Ustekinumab**
  - Does treatment with adalimumab or phototherapy lower vascular inflammation and improve lipid metabolism in patients with moderate to severe psoriasis? (NCT01553058)
  - Does treatment with ustekinumab lower vascular inflammation and improve lipid metabolism in patients with moderate to severe psoriasis (NCT02187172)

- **Cardiovascular Inflammation Reduction Trial (CIRT)**
  - Does methotrexate lower the risk of major vascular events in patients with a history of MI and diabetes or metabolic syndrome? (NCT01594333)
Probability of benefit vs harm

1. .0005% **HARM**: Lymphoma from Infliximab in RA compared to general population
2. 1.67% **BENEFIT**: Primary prevention of MI/Stroke statins
3. 2% **HARM**: Diabetes from statins
4. 50% **BENEFIT**: PASI 75 on Etanercept
5. 98% **No benefit**: Statins

Mariette X et al Ann Rheum Dis 2010 Feb;69(2):450-8
Dharamsi JW et al Br J Derm 2009;161:605-615
Topal SJ New York Times March 4 2012

Psoriasis Treatment Paradigm

**Mild Disease:**
- Typically < 5% BSA
- Minimal disability or affects on HrQOL

**Moderate-severe:**
- Typically ≥ 5% BSA
- Significant disability or low HrQOL

Topicals

Topicals
UV therapies
Traditional Orals
Injectable Biologics

Pariser DM et al. Arch Derm. 2007;143:239-242
Treatment of Moderate to Severe Psoriasis

- Treatment goals in clinical practice remain largely undefined
- Guideline goals:
  - European: PASI75 and DLQI $\leq 1$ (no effect)
  - Australasian: PASI75 and DLQI $\leq 5$ (small effect)
- Psoriasis non-treatment, under treatment, and treatment dissatisfaction remain significant problems in the US

Moderate-Severe Psoriasis MD-reported Outcomes: Clinical Trials

- Clinical trials primary endpoints focus on PASI75 and physician’s global assessment (PGA) of clear/almost clear
- Increasingly PASI 90 and 100 reported

Robinson A et al JAAD 2012; 66:369-75
Revicki DA et al Dermatology 2008; 216: 260-270
Torii H et al J Dermatol 2012; 39:253-259
Moderate-Severe Psoriasis Patient-Reported Outcomes: Clinical Trials

- DLQI asks about symptoms & feelings, daily activities, leisure, work/school, relationships, treatment
- Many other patient reported instruments available.

1st Line Treatment of Extensive Psoriasis: American Academy of Dermatology Guidelines

Menter, A et al. JAAD 2008;58:826-50
### Biologics and commonly used oral treatments for Psoriasis

#### NNT to Achieve PASI-75 at PEP

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tx (%)</th>
<th>PBO (%)</th>
<th>PEP (Wks)</th>
<th>NNT</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>35.5</td>
<td>18.9</td>
<td>16</td>
<td>5.88</td>
<td>7.5 mg to 25 mg weekly</td>
</tr>
<tr>
<td>Alefacept #</td>
<td>33</td>
<td>13</td>
<td>14</td>
<td>5</td>
<td>15 mg IM</td>
</tr>
<tr>
<td>Apremilast</td>
<td>32</td>
<td>5</td>
<td>16</td>
<td>3.7</td>
<td>30 mg bid</td>
</tr>
<tr>
<td>Efalizumab #</td>
<td>39</td>
<td>2.4</td>
<td>12</td>
<td>2.7</td>
<td>1 mg/kg/dose</td>
</tr>
<tr>
<td>Etanercept</td>
<td>49</td>
<td>4</td>
<td>12</td>
<td>2.2</td>
<td>50 mg biw</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>71</td>
<td>6.5</td>
<td>16</td>
<td>1.6</td>
<td>40 mg EOW</td>
</tr>
<tr>
<td>Infliximab</td>
<td>75.5</td>
<td>1.9</td>
<td>10</td>
<td>1.4</td>
<td>5 mg/kg</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>66</td>
<td>3</td>
<td>12</td>
<td>1.6</td>
<td>90 mg</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>81.6</td>
<td>4.5</td>
<td>12</td>
<td>1.3</td>
<td>300 mg</td>
</tr>
<tr>
<td>Brodalumab *</td>
<td>83.3</td>
<td>2.7</td>
<td>12</td>
<td>1.3</td>
<td>210 mg</td>
</tr>
<tr>
<td>Ixekizumab *</td>
<td>89.1</td>
<td>3.9</td>
<td>12</td>
<td>1.2</td>
<td>80 mg</td>
</tr>
</tbody>
</table>

Source: US FDA Package Inserts or Phase 3 Trials

# withdrawn *Not FDA approved

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**Fig. 1** New biologics and small molecules under development for the treatment of plaque psoriasis. Dendritic cells produce interleukins (IL)-12 and IL-23, implicated in TH1 and TH17 lymphocyte differentiation, respectively. IL-1, produced by activated macrophages is an important mediator of the inflammatory response. Tumour necrosis factor (TNF)-α, IL-17, IL-22 and IL-26 stimulate keratinocyte production of cytokines, chemokines and adhesion molecules, which, in turn, attract neutrophils and T lymphocytes, which leads to amplification of inflammation. Blocking targets of the new biologics are IL-33 (tildrakizumab and guselkumab), IL-17 (secukinumab and etanercept), and IL-17 receptor (brodalumab). Blocking targets of the small molecules are phosphodiesterase 4 (pimecrolimus) and Janus kinase (JAK) (tacrolimus and ruxolitinib). CTL01 is an A1 adenosine receptor agonist that downregulates the nuclear factor-κB signalling pathway.

Kofoed K, Skov L and Zachariae C New Drugs and Treatment Targets in Psoriasis Acta Derm Venereol 2015;95 133.139

Slide adapted from C. Leonardi, MD 3.25.15
Biologics and commonly used oral treatments for psoriasis NNT to achieve PASI-75 at PEP

<table>
<thead>
<tr>
<th>Treatment</th>
<th>NNT (treatment)</th>
<th>NNT (placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>5.9</td>
<td>10.9</td>
</tr>
<tr>
<td>Apremilast</td>
<td>3.7</td>
<td>6.7</td>
</tr>
<tr>
<td>Apremilast*</td>
<td>5.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Etanercept</td>
<td>2.7</td>
<td>5.7</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>1.6</td>
<td>3.6</td>
</tr>
<tr>
<td>Infliximab</td>
<td>1.4</td>
<td>3.4</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>1.6</td>
<td>3.6</td>
</tr>
<tr>
<td>Brodalumab</td>
<td>1.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Brodalumab*</td>
<td>1.6</td>
<td>3.6</td>
</tr>
<tr>
<td>Brodalumab**</td>
<td>1.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Brodalumab**</td>
<td>1.2</td>
<td>2.2</td>
</tr>
</tbody>
</table>

*Withdrawn
**Not FDA approved


20% of almost clear patients meet DLQI criteria for treatment change

<table>
<thead>
<tr>
<th>DLQI</th>
<th>Clear</th>
<th>Almost Clear</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ Moderate effect, N(%)</td>
<td>2 (2)</td>
<td>85 (20)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Biologics Used In Psoriasis
#### NNT to Achieve PASI-90 at PEP

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tx (%)</th>
<th>PBO (%)</th>
<th>PEP (Wks)</th>
<th>NNT</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>22</td>
<td>1</td>
<td>12</td>
<td>4.8</td>
<td>50 mg biw</td>
</tr>
<tr>
<td>Infliximab</td>
<td>45.2</td>
<td>0.5</td>
<td>10</td>
<td>2.2</td>
<td>5 mg/kg</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>45</td>
<td>2</td>
<td>16</td>
<td>2.3</td>
<td>40 mg EOW</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>36.7</td>
<td>2</td>
<td>12</td>
<td>2.9</td>
<td>90 mg</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>59.2</td>
<td>1.2</td>
<td>12</td>
<td>1.7</td>
<td>300 mg</td>
</tr>
<tr>
<td>Brodalumab*</td>
<td>73.3</td>
<td>0.9</td>
<td>12</td>
<td>1.4</td>
<td>210 mg</td>
</tr>
<tr>
<td>Ixekizumab*</td>
<td>70.9</td>
<td>0.5</td>
<td>12</td>
<td>1.4</td>
<td>80 mg</td>
</tr>
</tbody>
</table>

Source: US FDA Package Inserts or Phase 3 Trials

* Not FDA approved

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### Secukinumab – First IL-17 targeted treatment approved for psoriasis has rapid onset and high efficacy

IL-17 targeted treatments superior efficacy compared to ustekinumab: secukinumab example

Thaci D et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: 16 week results from the CLEAR study. Late Breaking Research. AAD March 2015.

IL-17 targeted treatments superior efficacy compared to ustekinumab: brodalumab example

PGA Clearance: real world vs. RCT

- Most patients fail to achieve long term disease control
- Durable response rates are much lower in clinical practice compared to short term RCTs

Impact of BMI on treatment effectiveness

- P for trend = 0.002
- Under or Normal Weight (BMI < 25)
- Overweight (25 ≤ BMI < 30)
- Obese (BMI ≥ 30)
Biologic survival in Denmark: DERMBIO Database

- N= 1867 treatment sequences in 1277 patients
- Ustekinumab has longest survival
- TNF survival
  - ETN 30 months
  - ADA 59 months
  - INF 44 months
- Protective factors
  - Male sex
  - Prior biologic exposure

Patient perspective on treatment discontinuation

Patient-reported reasons for the discontinuation of commonly used treatments for moderate to severe psoriasis

Howa Yeung, BS, Joy Wan, BA, Abby S. Van Voorhees, MD, Kristina Callis Duffin, MD, Gerald G. Krueger, MD, Robert E. Kalb, MD, Jamie D. Weisman, MD, Brian R. Sperber, MD, PhD, Bruce A. Brod, MD, Stephen M. Schleicher, MD, Bruce F. Bebo, Jr, PhD, Daniel B. Shin, MS,
Andrea B. Troxel, ScD, and Joel M. Gelfand, MD, MSc
Philadelphia and Hazelton, Pennsylvania; Salt Lake City, Utah; Buffalo, New York; Atlanta, Georgia; Colorado Springs, Colorado; and Portland, Oregon

Yeung H et al JAAD 2013; 68:64-72
Compared to methotrexate: adalimumab and etanercept more likely to be stopped due to loss of efficacy, less likely to be stopped due to side effects. Phototherapy more likely to be stopped because of cost.

Table IV. Adjusted odds ratios of citing specific discontinuation reasons

<table>
<thead>
<tr>
<th>Discontinuation Reason, OR (95% CI)</th>
<th>Methotrexate</th>
<th>Aldactone</th>
<th>Cyclosporine</th>
<th>Etanercept</th>
<th>Adalimumab</th>
<th>Etanercept</th>
<th>Methotrexate</th>
<th>Aldactone</th>
<th>Cyclosporine</th>
<th>Etanercept</th>
<th>Adalimumab</th>
<th>Or</th>
<th>FVCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did not work well enough</td>
<td>1.00 [ref]</td>
<td>1.56</td>
<td>0.75</td>
<td>1.28</td>
<td>1.74</td>
<td>0.59</td>
<td>0.99</td>
<td>0.67</td>
<td>0.97-2.86</td>
<td>0.46-1.25</td>
<td>0.89-2.83</td>
<td>1.11-5.75</td>
<td>0.30-1.15</td>
</tr>
<tr>
<td>Worked well at first but stopped working well</td>
<td>1.00 [ref]</td>
<td>0.86</td>
<td>1.43</td>
<td>5.19</td>
<td>2.10</td>
<td>2.07</td>
<td>0.88</td>
<td>1.09</td>
<td>0.46-1.62</td>
<td>0.77-2.68</td>
<td>3.21-8.33</td>
<td>1.20-3.67</td>
<td>0.95-4.51</td>
</tr>
<tr>
<td>Any side effects</td>
<td>1.00 [ref]</td>
<td>1.56</td>
<td>1.08</td>
<td>0.34</td>
<td>0.48</td>
<td>1.30</td>
<td>0.21</td>
<td>0.60</td>
<td>1.10-2.50</td>
<td>0.76-1.67</td>
<td>0.23-1.09</td>
<td>0.79-2.17</td>
<td>0.18-0.31</td>
</tr>
<tr>
<td>Cannot afford treatment</td>
<td>1.00 [ref]</td>
<td>2.90</td>
<td>1.47</td>
<td>1.45</td>
<td>0.83</td>
<td>0.89</td>
<td>7.03</td>
<td>2.40</td>
<td>0.76-5.61</td>
<td>0.51-4.20</td>
<td>0.08-3.10</td>
<td>0.29-3.22</td>
<td>0.21-3.82</td>
</tr>
</tbody>
</table>

- Mixed effects logistic regression
- Fixed effects – patient sociodemographics, psoriasis characteristics, and treatment variables
- Random effects – patient-level response clustering

Yeung H et al JAAD 2013; 68:64-72

Monthly Cost estimates to achieve PASI 75

Methotrexate, cyclosporine, and phototherapy yield lowest cost

Medication cost: Wholesale acquisition costs, range base on reported efficacy
Indirect costs (to patient) and adverse event costs not counted
Assumptions not tested with sensitivity analyses

Safety Concerns of Long-Term Treatment of Psoriasis with Traditional Systemic Therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Top Safety Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Cirrhosis; regular liver biopsies recommended for those with risk factors; category X*</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Kidney failure; use limited to 1 year</td>
</tr>
<tr>
<td>Acitretin</td>
<td>Category X* (3-year window); liver toxicity; hyperostosis</td>
</tr>
</tbody>
</table>

- Patient factors (e.g., women of child-bearing age, alcohol use, advanced age, comorbidities) may be contraindications for traditional therapies
- Rotational therapy advocated for those on traditional agents to limit long-term toxicity

*Not recommended for use in pregnancy; risks clearly outweigh benefits in pregnant women.


Selected Clinically Important Biologic Adverse Events

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Common &gt; 5%</th>
<th>Uncommon 0.1%-5%</th>
<th>Rare &lt; 0.1%</th>
<th>Black Box</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>Injection site reaction + ANA Elevated ALP, cholesterol</td>
<td>Neutralizing antibodies Serious Infections Allergic reactions Malignancy</td>
<td>Tuberculosis, Lupus like syndrome, Hypersensitivity, Hep B reactivation. Demyelination, Congestive heart failure, Pancytopenia</td>
<td>Serious infections: Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens Malignancy: Lymphoma and other malignancies, some fatal. Hepatosplenic T cell lymphoma</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Injection site reaction + ANA</td>
<td>Serious Infections Malignancy</td>
<td>Tuberculosis, Lupus like syndrome, Hypersensitivity, Hep B reactivation. Demyelination, Congestive heart failure, Pancytopenia</td>
<td>Serious infections: Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens Malignancy: Lymphoma and other malignancies, some fatal.</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Infusion reactions + ANA Elevated LFT Neutralizing antibodies</td>
<td>Hypersensitivity Serious Infections Malignancy</td>
<td>Severe hepatic injury, Tuberculosis, Lupus like syndrome, Hypersensitivity, Hep B reactivation. Demyelination, Congestive heart failure, Pancytopenia</td>
<td>Serious infections: Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens Malignancy: Lymphoma and other malignancies, some fatal. Hepatosplenic T cell lymphoma</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>None</td>
<td>Serious Infections Malignancy</td>
<td>Reversible posterior leukoencephalopathy</td>
<td>None</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>Nasopharyngitis</td>
<td>Muco-cutaneous Candida</td>
<td>Exacerbation of Crohn’s disease</td>
<td>None</td>
</tr>
</tbody>
</table>

Adapted from prescribing information 3.28.15
### Lymphoma rates in RA population treated with anti-TNF therapy: cohort studies

<table>
<thead>
<tr>
<th>Author</th>
<th>N TNF</th>
<th>SIR</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolfe</td>
<td>8,614</td>
<td>2.9 (1.7-4.9)</td>
<td></td>
</tr>
<tr>
<td>Wolfe</td>
<td>10,815</td>
<td>1.8 (1.5-2.2)</td>
<td>1.0 (0.6-1.8)</td>
</tr>
<tr>
<td>Wolfe</td>
<td>2,221</td>
<td>1.0 (0.5-2.0)</td>
<td></td>
</tr>
<tr>
<td>Askling</td>
<td>6,604</td>
<td>2.0 (1.0-3.5)</td>
<td>1.35 (0.8-2.11)</td>
</tr>
<tr>
<td>Askling</td>
<td>4,160</td>
<td>2.9 (1.3-5.5)</td>
<td>1.1 (0.6-2.1)</td>
</tr>
<tr>
<td>Geborek</td>
<td>7,57</td>
<td>11.5 (3.7-27)</td>
<td>5.0 (0.9-26)</td>
</tr>
<tr>
<td>Setoguchi</td>
<td>1,152</td>
<td>2.2 (1.7-2.9)</td>
<td>1.1 (0.5-2.4)</td>
</tr>
<tr>
<td>Mariette</td>
<td>19,037</td>
<td>2.3 (1.6-3.3)</td>
<td>ADA 4.7 (1.3-17.7)** INF 4.1 (1.4-12.5)**</td>
</tr>
</tbody>
</table>

Mariette X et al Ann of Rheum Dis 2011:70:1895-1904
• estimated **compared to etanercept

### TNF inhibitors associated with lower risks of cancer and serious infection in psoriasis compared to RA: Meta-analyses of RCTs

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cancer</th>
<th>Serious infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>OR 3.3 (1.2-9.1)</td>
<td>OR 2.0 (1.3-3.1)</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>OR 1.48 (0.71-3.09)</td>
<td>OR 0.70 (0.40-1.21)</td>
</tr>
<tr>
<td>Psoriasis Time to event</td>
<td>IRR 0.99 (0.51-1.90)</td>
<td>IRR 0.59 (0.35-0.99)</td>
</tr>
</tbody>
</table>

Dommasch ED et al JAAD 2011:64:1035-1050
Bongartz T et al JAMA 2006;295:2275-2285
Combination treatment

- Most common is to use combination of methotrexate + a biologic
  - May improve skin and joint outcomes
  - May decrease incidence of drug neutralizing anti-bodies to biologics
- Phototherapy often added in patients not responding adequately to systemic agents
  - Acitretin + phototherapy accelerates treatment response and lower cumulative dose of both

Menter et al Guidelines of care for the management of psoriasis and psoriatic arthritis JAAD 2011;65;137-74
Menter et al Guidelines of care for the management of psoriasis and psoriatic arthritis JAAD 2010;62;114-35

<table>
<thead>
<tr>
<th>Scenario</th>
<th>TNF</th>
<th>IL12/23</th>
<th>IL-17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long term data</td>
<td>Emerging</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>PsA</td>
<td>FDA approved</td>
<td>Phase III promising</td>
<td></td>
</tr>
<tr>
<td>Crohn’s s</td>
<td>FDA approved</td>
<td>Phase II promising</td>
<td>Warning</td>
</tr>
<tr>
<td>Associated with decreased MI and stroke</td>
<td>Yes</td>
<td>TBD</td>
<td>TBD</td>
</tr>
<tr>
<td>CHF</td>
<td>Warning</td>
<td>No warning</td>
<td>No warning</td>
</tr>
<tr>
<td>MS</td>
<td>Warning</td>
<td>No benefit or harm phase II</td>
<td>Promising phase II</td>
</tr>
<tr>
<td>Ease of administration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient is obese</td>
<td>Infliximab preferred</td>
<td>Weight based dosing</td>
<td>Flexible dosing</td>
</tr>
<tr>
<td>Rapid onset and highest efficacy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long term persistence</td>
<td></td>
<td></td>
<td>TBD</td>
</tr>
</tbody>
</table>

Treatment selection depends on many factors

= gold standard
Moderate-Severe Psoriasis
Conclusions

• Moderate to severe psoriasis is associated with serious impairment in HrQOL and a 5-year decrease in life expectancy
• Rapid expansion of treatment alternatives achieving greater efficacy and possibly improved safety (longer term data needed)
• Treatment selection remains highly dependent on individual patient characteristics and preferences