Management of Psoriasis and PsA Biologics

Pre-Activity Question 1
How confident are you in using biologic therapy to achieve remission or low disease activity psoriasis?

1. Very confident
2. Confident
3. Somewhat confident
4. Not confident

Pre-Activity Question 2
How confident are you in using biologic therapy to achieve remission or low disease activity in PsA?

1. Very confident
2. Confident
3. Somewhat confident
4. Not confident

Pre-Activity Question 3
For patients who do not achieve adequate efficacy, I most often:

1. Switch in class
2. Switch to a different MOA
3. Give the current therapy more time
4. Add-on another therapy
Psoriasis

**Biologics Approved for Psoriasis**

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
<th>MOA</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>etanercept</td>
<td>Enbrel</td>
<td>anti-TNFα</td>
<td>Amgen</td>
</tr>
<tr>
<td>adalimumab</td>
<td>Humira</td>
<td>anti-TNFα</td>
<td>AbbVie</td>
</tr>
<tr>
<td>infliximab</td>
<td>Remicade</td>
<td>anti-TNFα</td>
<td>Janssen</td>
</tr>
<tr>
<td>ustekinumab</td>
<td>Stelara</td>
<td>anti-p40</td>
<td>Janssen</td>
</tr>
<tr>
<td>secukinumab</td>
<td>Cosentyx</td>
<td>anti-IL17A</td>
<td>Novartis</td>
</tr>
</tbody>
</table>

**Etanercept Efficacy: Psoriasis**

- Mean Improvement in PASI Score (%)
- Patients with PGA of Clear or Almost Clear (%)


**Adalimumab Efficacy in Three Phase III Clinical Trials: PASI 75**


**Pathogenesis of Psoriasis**

**Infliximab Efficacy: Psoriasis**

- Dose: 5mg / kg IV
- PASI 50
- PASI 75
- PASI 90

I added the newest approved agent. It might be better to change the MOA of Stelara from anti-p40 to anti-IL12/23.

Benjamin Ehst, 5/12/2015
Ustekinumab: p40 inhibitor


Choosing a biologic for psoriasis

<table>
<thead>
<tr>
<th>biologic</th>
<th>PASI 75 at week 12</th>
<th>route</th>
</tr>
</thead>
<tbody>
<tr>
<td>infliximab</td>
<td>76% (week 10)</td>
<td>IV</td>
</tr>
<tr>
<td>ustekinumab</td>
<td>70%</td>
<td>SQ</td>
</tr>
<tr>
<td>adalimumab</td>
<td>68%</td>
<td>SQ</td>
</tr>
<tr>
<td>etanercept</td>
<td>46%</td>
<td>SQ</td>
</tr>
</tbody>
</table>

- Differ in efficacy, but no one biologic has a superior safety profile
- Psoriatic arthritis – choose TNFα-inhibitor
- CHF – choose ustekinumab
- Multiple sclerosis – choose ustekinumab
- Insurance company: “Patient must fail one of the following: MTX, acitretin, ….”

Comparing Efficacy of Biologics in Psoriasis

<table>
<thead>
<tr>
<th>% Patients Achieving Response</th>
<th>PASI 50</th>
<th>PASI 75</th>
<th>PASI 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supportive care</td>
<td>13.1(9.6,17.1)</td>
<td>4.3(2.9,6.2)</td>
<td>0.7(0.4,1.1)</td>
</tr>
<tr>
<td>Infliximab (5 mg/kg)</td>
<td>92.8(90.1,95.2)</td>
<td>80.8(75.7,85.8)</td>
<td>55.3(48.2,62.9)</td>
</tr>
<tr>
<td>Ustekinumab (45 mg)</td>
<td>88.8(85.2,91.9)</td>
<td>73.5(67.5,79.9)</td>
<td>46.5(38.7,52.4)</td>
</tr>
<tr>
<td>Ustekinumab (90 mg)</td>
<td>85.0(80.2,89.1)</td>
<td>72.2(69.3,75.1)</td>
<td>38.4(31.3,45.8)</td>
</tr>
<tr>
<td>Adalimumab (40 mg EOW)</td>
<td>84.8(79.2,88.7)</td>
<td>66.9(62.7,73.1)</td>
<td>38.1(30.0,45.0)</td>
</tr>
<tr>
<td>Etanercept (50 mg BiW)</td>
<td>74.4(69.6,79.3)</td>
<td>52.5(46.9,58.7)</td>
<td>24.9(20.5,30.1)</td>
</tr>
<tr>
<td>Etanercept (25 mg BiW)</td>
<td>61.6(55.4,68.0)</td>
<td>38.3(32.3,45.0)</td>
<td>15.0(11.4,19.3)</td>
</tr>
</tbody>
</table>

NOT in head to head trials, Meta analysis.


Notable points:
- Biologics differ in efficacy, but no single biologic has an overall superior safety profile.
- Psoriatic arthritis patients may benefit from TNFα-inhibitors.
- CHF patients should consider ustekinumab.
- Multiple sclerosis patients should consider ustekinumab.
- Insurance companies might require patients to fail one or more of the following: MTX, acitretin, etc.

Choosing a biologic for psoriasis

- Differ in efficacy, but no one biologic has a superior safety profile.
- Psoriatic arthritis patients may benefit from TNFα-inhibitors.
- CHF patients should consider ustekinumab.
- Multiple sclerosis patients should consider ustekinumab.
- Insurance companies might require patients to fail one or more of the following: MTX, acitretin, etc.
Slide 15

BDE4  could add the data for Cosentyx
Benjamin Ehst, 5/12/2015

Slide 16

BDE5  again, could add the data for Cosentyx. Also would see if Dr Meese agrees with the statement of choosing TNF inhibitor for PsO patients with PsA.
Benjamin Ehst, 5/12/2015
IL-17 Inhibitors: Mechanisms of Action

Secukinumab
Ixekizumab
Brodalumab

Secukinumab (anti-IL17A): Psoriasis

Ixekizumab (anti-IL17A): Psoriasis

Brodalumab (anti-IL-17RA): Psoriasis

Secukinumab (anti-IL17A): Psoriasis

Emerging IL17 inhibitors for psoriasis

<table>
<thead>
<tr>
<th>Generic name</th>
<th>MOA</th>
<th>PASI 75 Week 12</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>secukinumab</td>
<td>anti-IL17a</td>
<td>82%</td>
<td>Novartis</td>
</tr>
<tr>
<td>ixekizumab</td>
<td>anti-IL17a</td>
<td>80%</td>
<td>Eli Lilly</td>
</tr>
<tr>
<td>brodalumab</td>
<td>anti-IL17a receptor</td>
<td>82%</td>
<td>Amgen</td>
</tr>
</tbody>
</table>

Efficacy of IL-17 Inhibitors in Plaque Psoriasis

Secukinumab (AIN457)

Ixekizumab (LY2439821)

Brodalumab (AMG827)


Drug administration was sub-cutaneous in all trials shown
Intravitreal administration is also under investigation

Secukinumab (anti-IL17A): Psoriasis

BDE6


Brokalumab (anti-IL-17RA): Psoriasis

120, 140, or 210 mg at weeks 0, 1, and 2, then every other week -or- 280 mg monthly


PM6

PM6  Check on reference 2 for published manuscript
  admin, 10/12/2014

Slide 27

BDE6  I'd replace this slide with the PASI-75 results from the phase III studies (in NEJM article).
  Benjamin Ehst, 5/12/2015
Psoriatic Arthritis

PsA Treatment: GRAPPA Evidence Review

Biologics for Psoriasis Current and Emerging

<table>
<thead>
<tr>
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<th>MOA</th>
<th>PASI 75 Week 12</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>etanercept</td>
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<td>46%</td>
<td>SQ</td>
</tr>
<tr>
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<td>anti-TNFα</td>
<td>68%</td>
<td>SQ</td>
</tr>
<tr>
<td>ustekinumab</td>
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<td>IV</td>
</tr>
<tr>
<td>Golimumab</td>
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<td>76% (week 10)</td>
<td>IV</td>
</tr>
<tr>
<td>Brodalumab</td>
<td>anti-IL17a receptor</td>
<td>82%</td>
<td>SQ</td>
</tr>
<tr>
<td>Lebrikizumab</td>
<td>anti-IL17a</td>
<td>80%</td>
<td>SQ</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>anti-IL17a</td>
<td>82%</td>
<td>SQ</td>
</tr>
</tbody>
</table>

Current and Emerging Biologics for Psoriasis

Bioavailability: etanercept: 46% SQ; adalimumab: 68% SQ; ustekinumab: 70% SQ; infliximab: 76% IV; Golimumab: 76% IV; Brodalumab: 82% SQ; Secukinumab: 82% SQ

PsA Treatment: GRAPPA Evidence Review

Adalimumab 213

Corticosteroids

Topical

Physiotherapy

Psoralen UVA/UVB

DMARDs (MTX, CsA, SSZ, Leflunomide)

Biologics (anti-TNF antagonists)

*Based on data from only placebo-controlled trials (used as surrogate for PsA spondylitis).


EULAR Recommendations for the Management of Psoriatic Arthritis

Baseline Characteristics of Patients in Active Treatment Arms of anti-TNF Phase 2-3 Trials in PsA

<table>
<thead>
<tr>
<th>Trial</th>
<th>ADA DAPT N=151</th>
<th>IFX IMPACTII N=146</th>
<th>ETN Phase III N=101</th>
<th>ETN PRESTA N=146</th>
<th>USTKNB (phase II) N=101</th>
<th>GLM N=146</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>49</td>
<td>47</td>
<td>46</td>
<td>47</td>
<td>49</td>
<td>47</td>
</tr>
<tr>
<td>PsA yrs</td>
<td>9.6</td>
<td>8.0</td>
<td>9.2</td>
<td>7.0</td>
<td>5.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Weight</td>
<td>86</td>
<td>86</td>
<td>86</td>
<td>82.9</td>
<td>82.9</td>
<td>82.9</td>
</tr>
<tr>
<td>SJC, N</td>
<td>14</td>
<td>14</td>
<td>16</td>
<td>12.5</td>
<td>8.5</td>
<td>13.2</td>
</tr>
<tr>
<td>TJC, N</td>
<td>25</td>
<td>25</td>
<td>20</td>
<td>19.2</td>
<td>17.8</td>
<td>22.8</td>
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<tr>
<td>WAIQ, N</td>
<td>1.0</td>
<td>1.1</td>
<td>1.1</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>1.4</td>
<td>2.1</td>
<td>2.2</td>
<td>0.9</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Previous DMARDs</td>
<td>1.5</td>
<td>1.7</td>
<td></td>
<td></td>
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<tr>
<td>Enthesitis, %</td>
<td>39</td>
<td>38</td>
<td>46</td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dactylitis, %</td>
<td>41</td>
<td>43</td>
<td>37</td>
<td>46</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PsA: Psoriatic Arthritis; ADA: adalimumab; IFX: infliximab; ETN: etanercept; GLM: golimumab; USTKNB: ustekinumab; SJC: spine involvement; TJC: joint involvement; WAIQ: work activity index quality; CRP: C-reactive protein; DMARD: disease-modifying antirheumatic drug

Anti-TNF Therapies in PsA: ACR and PASI Responses

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>ACR20 %</th>
<th>ACR50 %</th>
<th>ACR70 %</th>
<th>PASI75 %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rx</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>Rx</td>
</tr>
<tr>
<td>Adalimumab 213</td>
<td>315</td>
<td>58</td>
<td>14</td>
<td>38</td>
<td>4</td>
</tr>
<tr>
<td>Cetolizumab 3</td>
<td>406</td>
<td>58</td>
<td>24</td>
<td>36</td>
<td>11</td>
</tr>
<tr>
<td>Etanercept 2</td>
<td>60</td>
<td>74</td>
<td>14</td>
<td>48</td>
<td>5</td>
</tr>
<tr>
<td>Etanercept 3</td>
<td>205</td>
<td>59</td>
<td>15</td>
<td>38</td>
<td>4</td>
</tr>
<tr>
<td>Golimumab</td>
<td>406</td>
<td>52</td>
<td>8</td>
<td>32</td>
<td>35</td>
</tr>
<tr>
<td>Infliximab 2</td>
<td>100</td>
<td>69</td>
<td>8</td>
<td>49</td>
<td>9</td>
</tr>
<tr>
<td>Infliximab 3</td>
<td>200</td>
<td>58</td>
<td>11</td>
<td>36</td>
<td>3</td>
</tr>
</tbody>
</table>

*Based on data from only placebo-controlled trials (used as surrogate for PsA spondylitis).


References:

Anti-TNFs in PsA: Other Outcomes

- **Enthesitis**
  - ~60-75% improvement
  - Assessment methods: 4-point, MASES, Leeds, SPARCC
- **Dactylitis**
  - ~60% improvement
  - Assessment methods: Count, score, Leeds dactylometer
- **Function**
  - Significant improvement achieved as assessed by HAQ
- **QOL**
  - Significant improvements in SF-36, PsAQOL, DLQI, EQ-5D
- **Fatigue**
  - Significant improvement observed


Current RA Therapies – Use in PsA?

- **IL-1 Inhibitors,** e.g. Anakinra (Kineret) – not effective
- **Co-stimulatory blockade:** Alefacept (Amevive) (LFA3-CD2), Abatacept (CTLA4Ig) (B7-CD28)
- **B cell ablators and modulators** (minimally effective)


Abatacept: Effect of Prior Anti-TNF Therapy on ACR20 Response at Day 169

Abatacept: PASI 50 Response

Emerging Biologic Therapies for PsA

- **IL-12-23i**
  - Ustekinumab highly effective in psoriasis, modest in PsA
  - Bi_fillumab – discontinued because of CV safety concerns
- **IL-17i**
  - Importance of IL23R and TH17 cell in PsA
  - Outstanding efficacy in psoriasis, data in PsA emerging
- **IL-6 and IL-6Ri**
  - IL-6 richly expressed in psoriasis plaques and PsA synovium
  - Background concern about potential for LFT/lipid increase
  - May be used as monotherapy without background MTX
  - Plus/minus effectiveness of tocilizumab in PsA case reports
  - Data from Phase 2 trial of cimzilizumab in PsA pending

### Ustekinumab (IL12/23) in Psoriatic Arthritis: ACR20/50/70 Responders at Week 24

**Dosing schedule:** weeks 0, 4 and q12 weeks, thereafter.

**ACR20:** 22.8% | **ACR50:** 8.7% | **ACR70:** 2.4% | **PASS75:** 14.2%

**PSUMMIT I and PSUMMIT II**

**Comparisons of Efficacy Results at Week 24 (Anti TNF Naive)**

**PSUMMIT II**

**Efficacy Results at Week 24 in Anti TNF Experienced Patients**

**Brodalumab in PsA: ACR 20 and 50 Responses through 52 Weeks: Observed Analysis**

**Brodalumab in PsA: Mean Change in DAS28 to 52 Weeks: Observed Analysis**
**Brodalumab in PsA: Mean Change from Baseline in Dactylitis and Enthesitis through Week 52: Observed Analysis**

- **Enthesitis**
  - Brodalumab 280 mg/brodalumab 280 mg
  - Brodalumab 280 mg Q2W
  - PBO/brodalumab 280 mg
  - Brodalumab 140 mg/brodalumab 280 mg
  - Brodalumab 140 mg Q2W

- **Dactylitis**
  - Brodalumab 280 mg/brodalumab 280 mg
  - Brodalumab 280 mg Q2W
  - PBO/brodalumab 280 mg
  - Brodalumab 140 mg/brodalumab 280 mg
  - Brodalumab 140 mg Q2W

Mean (SE) Score Change from Baseline:

<table>
<thead>
<tr>
<th></th>
<th>Week 52</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline score</td>
<td>4.0</td>
<td>4.1</td>
</tr>
</tbody>
</table>

- **Baseline score: 4.0
- n = 21
- 28
- 29
- 25
- 36
- 38
- 30

**Cytokine Targets in Psoriasis Therapy**

- TNFα
- IL-17
- IL-22
- IFNα
- P19
- IL-10

**Biologic Therapy: Safety Issues**

- Infection
- TB/Opportunistic infections
- Neoplasm/lymphoma/skin cancer
- Autoimmune/lupus/MS/psoriasis
- CHF
- Administration reactions
- Vaccination issues

**Conclusions**

- Biologic therapy has revolutionized the treatment of psoriasis and PsA
- Achievement of remission or low disease activity is now achievable
- For patients who don’t achieve adequate efficacy, lose efficacy, or cannot tolerate med, switching in class or different MOA can occur
- Safety is an issue and close monitoring is necessary

**Special Issues**

- Durability of biologic therapy effectiveness
  - Immunogenicity
  - Tolerability and safety
- Cost
- Patient acceptability
- Biosimilars

**Post-Activity Question 1**

How confident are you in using biologic therapy to achieve remission or low disease activity psoriasis?

1. Very confident
2. Confident
3. Somewhat confident
4. Not confident
Post-Activity Question 2

How confident are you in using biologic therapy to achieve remission or low disease activity in PsA?
1. Very confident
2. Confident
3. Somewhat confident
4. Not confident

Post-Activity Question 3

For patients who do not achieve adequate efficacy, I plan to:
1. Switch in class
2. Switch to a different MOA
3. Give the current therapy more time
4. Add-on another therapy