Management of Psoriasis and PsA Biologics

Speakers

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Choosing a Biologic Therapy for Psoriasis

Does Patient have PsA?

Yes and failed NSAIDS

MTX, TNF BLOCKER, MTX+TNF BLOCKER
Etanercept, Infliximab, Adalimumab, Golimumab, Ustekinumab, Certolizumab

Comorbidities to TNF Blockade

No

Psoriasis

Comparing Efficacy of Biologics in Psoriasis

% Patients Achieving Response

<table>
<thead>
<tr>
<th></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 (2.8, 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, 78.9)</td>
<td>45.5 (38.7, 52.4)</td>
</tr>
<tr>
<td>Ustekinumab (90 mg)</td>
<td>85.0 (80.2, 89.1)</td>
<td>67.2 (60.1, 73.8)</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>68.0 (58.7, 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 (25mg BIW)</td>
<td>61.6 (55.4, 68.6)</td>
<td>38.3 (32.3, 45.0)</td>
<td>15.0 (11.4, 19.3)</td>
</tr>
</tbody>
</table>

*FDA approved for the treatment of psoriatic arthritis. †FDA approved for the treatment of plaque psoriasis.

NOT in head to head trials, Meta analysis

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


PASI 50 PASI 75 PASI 90

Dose: 5mg / kg IV

Per Protocol Intention to Treat

Infliximab Efficacy: Psoriasis

T Cell Differentiation Pathways

T cell membrane

IL-23

IL-17

IL-12

INF

T cell proliferation

Ustekinumab Inhibits IL-12 and IL-23 by Targeting the p40 Subunit

Ustekinumab Efficacy: Psoriasis

PASI 75 PGA 0 or 1

PASI 90 PASI 50


IL-32

IL-22

IL-12Rβ1

IL-12Rβ2

p19

p35

p40

IL-17 Inhibitors: Mechanisms of Action

- Secukinumab (anti-IL-17A): Psoriasis
  - Dosed weeks 0, 2, 4, 8, and 12. Primary endpoint PASI 75 at week 12

- Ixekizumab (anti-IL17A): Psoriasis
  - Dosed weeks 0, 2, 4, 8, and 12. Primary endpoint PASI 75 at week 12

- Brodalumab (anti-IL-17RA): Psoriasis
  - 70, 140, or 210 mg at weeks 0, 1, and 2, then every other week -or- 280 mg monthly

- Secukinumab (AIN457)2
  - n=125

- Brodalumab (AMG827)3

- Ixekizumab (LY2439821)1
  - n=141

- Secukinumab (AIN457)2


Efficacy of IL-17 Inhibitors in Plaque Psoriasis

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

Psoriatic Arthritis

PsA Treatment: GRAPPA Evidence Review

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

<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>ADA ADEPT 2/3</td>
<td>315</td>
<td>58</td>
<td>14</td>
<td>36</td>
<td>4</td>
</tr>
<tr>
<td>Certolizumab 3</td>
<td>405</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>405</td>
<td>52</td>
<td>8</td>
<td>32</td>
<td>3.5</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>

Anti-TNF Therapies in PsA: ACR and PASI Responses

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, DLOI, 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 (Amrheinve) (LFA3-CD2), Abatacept (CTLA4Ig) (B7-CD28)
- B cell ablators and modulators (minimally effective)
Abatacept in PsA
ACR Responses at Day 169

Error bars represent 95% CI; *P<.022; †P=.006; ‡P=.121 vs placebo.

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

Error bars represent 95% CI.

Abatacept: PASI 50 Response

PASI 50 response: ≥50% improvement in PASI score in patients with ≥3% BL body surface area affected with psoriasis

Emerging Biologic Therapies for PsA

- IL-12/23i
  - Ustekinumab highly effective in psoriasis, modest in PsA
  - Birakinumab – 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 clazakizumab 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.
*p<.001.

PSUMMIT I and PSUMMIT II
Comparisons of Efficacy Results at Week 24 (Anti TNF Naive)

PSUMMIT I
PSUMMIT II

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

**ACR Response (%)**

<table>
<thead>
<tr>
<th>Group</th>
<th>ACR30</th>
<th>ACR50</th>
<th>ACR70</th>
<th>PASI75</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO (n=62)</td>
<td>14.5</td>
<td>6.1</td>
<td>5.0</td>
<td>5.2</td>
</tr>
<tr>
<td>UST 45 mg (n=60)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UST 90 mg (n=58)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Values are n (%) unless otherwise stated.*

**Mean (SE) Score Change**

- **Dactylitis**
  - PBO: -2.13
  - Brodalumab 140 mg Q2W: -0.73
  - Brodalumab 280 mg Q2W: -1.73

- **Enthesitis**
  - PBO: -2.0
  - Brodalumab 140 mg Q2W: 0.10
  - Brodalumab 280 mg Q2W: 0.06

*Values are n (%) unless otherwise stated.*

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**Safety Summary Through Week 24**

<table>
<thead>
<tr>
<th>Event</th>
<th>PBO (n=31)</th>
<th>UST 45 mg (n=83)</th>
<th>UST 90 mg (n=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deaths</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Serious Infections</strong></td>
<td>1 (0.6%)</td>
<td>1 (1.2%)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>DVT/PE</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>0</td>
<td>1 (1.2%)</td>
<td>1 (0.9%)</td>
</tr>
</tbody>
</table>

*Values are n (%) unless otherwise stated.*

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**Mean Change in DAS28 to 52 Weeks: Observed Analysis**

- **PBO**: 1.40
- **Brodalumab 140 mg Q2W**: 1.70
- **Brodalumab 280 mg Q2W**: 2.13

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**Biologic Therapy: Safety Issues**

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

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

Cytokine Targets in Psoriasis Therapy

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

Questions & Answers