Biologics in Psoriasis

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Disclosures

• Consultancy services for Celgene, Centocor, Almirall, Amgen, Pfizer, Philips, Abbott, Eli Lilly, Galderma, Novartis, Janssen Cilag, Leo Pharma, Sandoz, Mitsibishu, Sandoz

• Clinical trials for: Basilea, Pfizer, Eli Lily, Amgen, Abbvie, Philips Lighting, Janssen Cilag, Leo Pharma
Clinical Manifestations of Plaque Psoriasis
Special skin locations
Comorbidities of plaque psoriasis:

- Psoriatic arthritis occurs in about 30% of patients with psoriasis.
- Psoriasis has been associated with an increased risk of cardiovascular disease and cardiovascular risk factors.
- Psoriasis has also been associated with an increased risk for Crohn’s disease, depression and sleep disorder.

The Traditional Stepwise Approach

OTC products

Rx topical agents

Phototherapy

Systemic therapy
- Methotrexate
- Ciclosporin
- Acitretin
- Apremilast

Biologic therapy
- Anti-TNF
- Anti-IL-12/23
- Anti-IL-17
- Anti-IL-23

Options for long-term treatment
Arthritis

Adapted from Leonardi CL. Available at: http://www.medscape.org/viewarticle/586198. Accessed October 2017
Biologic Drugs

FDA and EMA approved biologic therapies for moderate-to-severe plaque psoriasis:
1. TNF-a antagonists (adalimumab, etanercept, and infliximab),
2. IL-12/23p40 inhibitor (ustekinumab)
3. IL-17A inhibitor (secukinumab, ixekizumab).
4. IL-17 receptor antagonist
5. IL-23p19 inhibitor (guselkumab) (FDA July 2017)
Anti TNF

adalimumab, etanercept, and infliximab biosimilars
Multiple Targets in the Treatment of Psoriasis;

Multiple Biologics Available

Short Term-Efficacy Biologics

PASI 75 and PASI 90
Etanercept, Adalimumab und Ustekinumab (week 12)
Infliximab (week 10)

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dosage</th>
<th>PASI 75 (%)</th>
<th>PASI 90 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>25 mg</td>
<td>34</td>
<td>11</td>
</tr>
<tr>
<td>Etanercept</td>
<td>50 mg</td>
<td>49</td>
<td>21</td>
</tr>
<tr>
<td>Infliximab</td>
<td>5 mg/kg</td>
<td>80</td>
<td>57</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>40 mg</td>
<td>68</td>
<td>37</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>45 mg</td>
<td>67</td>
<td>42</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>90 mg</td>
<td>76</td>
<td>51</td>
</tr>
</tbody>
</table>

Mean % PASI improvement vs. time for Placebo and Adalimumab.

- **Placebo**: n=102
- **Adalimumab**: n=55

- PASI 75 to 100
- PASI 50 to <75
- <PASI 50

Weeks: 0, 12, 24, 36, 48, 60, 72, 84, 96, 108.

**OLE Week**

**Radboudumc**
IL-12/23p40 inhibitor

Ustekinumab
Multiple Targets in the Treatment of Psoriasis;

Multiple Biologics Available

PHOENIX 1

Long-term efficacy through Year 5

![Graph showing percentage of patients achieving PASI 75 over weeks.](image)

*Note: Placebo cross-over patients are included beginning at Week 24 (i.e., 12 weeks after UST treatment). Analyses were not conducted between Weeks 40 and 76 when the majority of the population was withdrawn from treatment per study design. Analyses resumed at Week 76 when about half of the withdrawn patients had reinitiated UST for at least 12 weeks. Patients who reinitiated treatment after Week 76 were re-included after at least 12 weeks of re-treatment.

Side effects of anti TNF and anti IL12/23 in psoriatic patients

- Upper respiratory track infections
- Opportunistic infections (very rare in data base)
- Malignancies (no clear sign in data base)
- Congestive heart disease
Anti IL-17

1. IL-17A inhibitor (secukinumab, ixekizumab).
2. IL-17 receptor antagonist (brodalumab)
Multiple Targets in the Treatment of Psoriasis;

Multiple Biologics Available

Differences Between Targeting Th17 Cells and IL-17A

Th17 cells produce many different cytokines

- IL-17A, IL-21, GM-CSF, IL-22, IL-17F, IL-26, CCL20

IL-17A is produced by many different cells besides Th17

- LTi cell
- Th17 cell
- NKT cells
- ILC3
- NK cells
- γδ T-cells
- CD8+ T-cell
- Mast cell

CD=Cluster of Differentiation; LTi=Lymphoid Tissue Inducer; NK=Natural Killer; NKT=Natural Killer T.

PASI 75 Response for IL-17 Inhibitors

Secukinumab: A Fully Human IL–17A-selective Monoclonal Antibody

- Fully human IgG1k-Antibody
- Created using Medarex-mice
- Affinity ~200 pM for human IL-17A
- Low serum clearance rate and long terminal half-life (~27 days)

Ig, Immunoglobulin; IL, Interleukin
Data on File
CLEAR Trial

SAEs: No Clinically Meaningful Differences Between Groups

Low Incidence of Serious Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>SEC 300 mg (n = 1410)</th>
<th>SEC 150 mg (n = 1395)</th>
<th>PBO (n = 793)</th>
<th>ETAN (n = 323)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SAE, n (IR)</td>
<td>85 (7.42)</td>
<td>76 (6.80)</td>
<td>15 (7.54)</td>
<td>20 (7.01)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3 (0.25)</td>
<td>3 (0.26)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>1 (0.08)</td>
<td>2 (0.18)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>1 (0.08)</td>
<td>2 (0.18)</td>
<td>2 (0.99)</td>
<td>1 (0.34)</td>
</tr>
<tr>
<td>Abscess bacterial</td>
<td>0 (0.00)</td>
<td>3 (0.26)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>Appendicitis</td>
<td>2 (0.17)</td>
<td>1 (0.09)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1 (0.08)</td>
<td>1 (0.09)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>Hypertensive crisis</td>
<td>2 (0.17)</td>
<td>1 (0.09)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>1 (0.09)</td>
<td>1 (0.09)</td>
<td>4 (1.99)</td>
<td>1 (0.34)</td>
</tr>
<tr>
<td>Sciatica</td>
<td>2 (0.18)</td>
<td>2 (0.18)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
</tr>
</tbody>
</table>

Most frequent SAEs ≥0.15 per 100 patient years; entire treatment period (52 weeks)

Treatment-emergent SAEs are summarized in this table. IR = incidence rate per 100 patient years.
For patients with event, exposure time is censored at time of first event.
Candidiasis: Non-serious Superficial Mucocutaneous Infections

*Entire Treatment Period – Exposure Adjusted (52 Weeks)*

- Higher frequency of non-serious Candida infections reported with 300 mg
- No cases of systemic or invasive infections
  - Majority of infections mild to moderate
  - None serious; all responded to conventional treatment
  - No discontinuations

### Candida infections

<table>
<thead>
<tr>
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<th>PBO (n = 793)</th>
<th>ETAN (n = 323)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on all AEs</td>
<td>41 (3.55)</td>
<td>21 (1.85)</td>
<td>2 (1.00)</td>
<td>4 (1.37)</td>
</tr>
<tr>
<td>Based on SAEs</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
</tr>
</tbody>
</table>

Gaffen et al 2011; Miller and Cho 2011
Interleukin-17 inhibition: role in psoriasis and inflammatory bowel disease

- IL-17-A inhibition, IL-17RA inhibition and IL-17 knockout led to induction or exacerbation of colitis in mouse models.
- Anti-IL-17 medications are associated with IBD exacerbation.
- Caution should be used in prescribing these medications in patients with diagnosed IBD or personal history suggestive of IBD.

Side effects of anti IL-17 in psoriatic patients

- Upper respiratory track infections
- Opportunistic infections (no signal)
- Malignancies (no signal)
- Candidiasis
- Aggravation IBD
Anti IL-17

1. IL-17A inhibitor (secukinumab, ixekizumab).
2. IL-17 receptor antagonist (brodalumab)

Class effect / Molecule effect
Anti-IL-23
Risankizumab
Guselkumab
Tildrakizumab
Multiple Targets in the Treatment of Psoriasis;

Multiple Biologics Available

• Adapted from Nestle F et al. N Engl J Med. 2009;361:496-509
Molecular Characteristics of Risankizumab

- Total molecular mass of ~148 kDa
- Two framework mutations in Fc region to reduce binding to Fcγ receptor and complement (FcRn binding preserved)
- Two binding sites for IL-23p19
- In a Phase 1 study, half-life ranged from 20 to 28 days after a single IV administration

References:
1. Singh S et al. mAbs 2015;7:778
Rizankizumab PASI90 Response (NRI)


*18 mg risankizumab only given once at Week 0. Analysis includes all patients who were randomised and who received at least one dose of assigned therapy during the study with non-responder imputation.
Side effects of anti IL-23

- Upper respiratory track infections
- Opportunistic infections (no signal)
- Malignancies (no signal)
- Candidiasis (no signal)
- Aggravation IBD (no signal)
Psoriasis Patients Treated With Biologics and Methotrexate Have a Reduced Rate of Myocardial Infarction: A Collaborative Analysis Using International Cohorts.

Gulliver WP, Young HM, Bachelez H, et al
Value of biologics in psoriasis is a sustainable disease control more than skin deep

Highly effective longterm control of skin manifestations of psoriasis
Preventing development of comorbidity