Psoriasis Therapies:
Choosing the Correct Drug

Bruce Strober, MD, PhD

Professor and Chair
Department of Dermatology
UConn Health Center
Farmington, CT
July 30, 2017
DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

Bruce Strober, MD, PhD

Consultant and Advisory Boards – AbbVie, Amgen, Astra Zeneca, Celgene, Dermira, Janssen, Leo, Eli Lilly, Cutanea-Maruho, Medac, Novartis, Pfizer, Regeneron, Sanofi-Aventis, Sun Pharma, Boehringer Ingelheim, UCB
Investigator – AbbVie, Amgen, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Eli Lilly, Janssen, Merck, Sun Pharma, Celgene
Scientific Director – CORRONA Psoriasis Registry
Grant Support to the University of Connecticut for Fellowship Program – AbbVie, Janssen
Key Points

• Choose therapy based on individual patient characteristics
• Ps treatment is NOT stepwise (i.e. not required to fail on topicals)
• One drug or modality may succeed when others fail
• Combination therapy may be desirable in some patients
Baseline

PASI Score = 43.9

Week 12

PASI Score = 0.4
Ultraviolet Phototherapy

- Effective and safe
- No psoriatic arthritis
- Practical for the patient
Why Do We Need to Know About Methotrexate and Cyclosporine?

- Effective and safe if used correctly
- Cost-effective and FDA-approved for psoriasis
- Not all patients can receive biologic therapy
- Biologic therapies may fail as monotherapy, and succeed in combination with traditional systemics
- Rescue therapies in tough clinical scenarios
Infliximab vs MTX

PASI 75 response by visit (intent-to-treat population)
Patients achieving <PASI 50 by week 16 were permitted to switch treatment groups

Methotrexate: When Do I Use It?

- Medicare patients
- Lack of health insurance
- Psoriatic arthritis
- Pediatric psoriasis
- Prior to a biologic therapy
- Combined with a biologic therapy
Cyclosporine Study: “Clear or Almost Clear” at Week 8

- Placebo: 0%
- CyA 3.0 mg/kg (n=30): 36%
- CyA 5.0 mg/kg (n=30): 65%
- CyA 7.5 mg/kg (n=30): 80%

Cyclosporine: When Do I Use It?

- Severe patients in need of quick response
- Pregnancy
- Patients who fail other therapies
- Prior to biologic therapies
- Combined at lower doses with a biologic therapy
Etanercept
TNF-α Blocker
Etanercept: PASI 75 Response

[Graph showing PASI 75 response at 12 and 24 weeks for different treatment groups.]

- Placebo/etanercept 25 mg BIW (n=166)
- Etanercept 25 mg QW (n=160)
- Etanercept 25 mg BIW (n=162)
- Etanercept 50 mg BIW (n=164)

Placebo switched to 25 mg BIW

% of Patients

1P < 0.001 vs placebo

Etanercept
TNF-α Blocker

Pros

• Well-tolerated and effective (PI: PASI 75 45-54%)
• Self-injectable; SC
• Treats PsA
• Pregnancy safe
• Extensive post-marketing experience
• Pediatric indication
• No contraindication in IBD
• May benefit patients with CV co-morbidity risks
Etanercept
TNF-α Blocker

Cons

• Lowest Ps efficacy of the 3 approved TNF-α inhibitors
• Step down dosing (50 mg BIW to 50 mg QW) results in loss of response
• Fixed dose loses response over time
• Lower efficacy in heavier patients (>100 kg)
• Slight risk of TB reactivation – test for latent/active TB required
• Contraindicated in CHF, MS, active infection
• Very rare lupus-like syndrome
Etanercept
TNF-α Blocker

Who gets this drug:

• Any patient with moderate-to-severe psoriasis, though lower efficacy moves it down list
  • 1st line drug

• Psoriatic arthritis

• Pediatric (children and adolescents) → should be first biologic chosen for this group

• No personal history of MS or severe CHF
Adalimumab
TNF-α Blocker
Wk 24 results represent pooling of efficacy outcomes from Period B and OLE

* p<0.001, adalimumab vs. placebo

ITT: Patients with missing PASI scores were considered non-responders
Dosing: 80 mg first week, 40 mg second week, 40 mg every other week thereafter

Adalimumab
TNF-α Blocker

Pros

• Well-tolerated and highly effective SC; QOW; (PI: PASI 75 71%)
• Treats PsA
• Pregnancy safe
• Extensive post-marketing experience
• Pediatric indication for JIA (PI: > 4 years) and for psoriasis in Europe
• No contraindication in IBD
• May benefit patients with CV co-morbidity risks
Adalimumab
TNF-α Blocker

Cons

• Fixed dose loses response over time; higher immunogenicity
  • Mitigated by concomitant MTX

• Some loss of efficacy in heavier patients (>100 kg)

• Elevated risk of TB reactivation - test for latent/active TB required

• Contraindicated in patients with CHF, MS, active infection

• Very rarely lupus-like syndrome
Adalimumab
TNF-α Blocker

Who gets this drug:

• Any patient with moderate-to-severe psoriasis
  • 1st line drug
• Psoriatic arthritis
• Pediatric (children and adolescents)
• No personal history of MS or severe CHF
Infliximab
TNF-α Blocker
Infliximab PASI 75 Results over 50 weeks

Infliximab
TNF-α Blocker

Pros

• Superlatively effective TNF inhibitor (PI: PASI 75 78%)
• Treats PsA
• Dosed by weight, comparable efficacy for all weights
• Pregnancy safe
• Extensive post-marketing experience
• No contraindication for IBD and has pediatric indication for Crohn’s disease
• May benefit patients with CV co-morbidity risks
Infliximab
TNF-α Blocker

Cons

• Intravenous; must monitor for infusion reactions
• Loss of efficacy over time (mitigated by concomitant MTX)
• Monitor LFTs
• Higher risk of TB reactivation – test for latent/active TB required
• Contraindicated in patients with CHF, MS and active infection
• Very rarely lupus-like syndrome
Infliximab
TNF-α Blocker

Who gets this drug:

• Any patient with moderate-to-severe psoriasis, likely having failed at least 2 other biologics, and previous response to 2 TNF-inhibitors who then lost response

• Obese patients who require weight-based dosing

• Psoriatic arthritis

• Pediatric (children and adolescents) who have failed multiple other modalities

• No personal history of MS or severe CHF
Ustekinumab
IL-12/23 inhibitor
Ustekinumab: PASI 75 response

*p<0.001 vs. placebo

n=410
n=409
n=411
Pros

- Well tolerated and highly effective
- Infrequently dosed
- No contraindication in CHF, MS, or IBD
- Low risk of TB reactivation
- Unpredictable positive effect on psoriatic arthritis
  - Likely less effective than TNF-inhibitors, and, perhaps, IL-23 & IL-17 inhibitors
Ustekinumab
IL-12/23 Blocker

Cons

• Lower efficacy in psoriatic arthritis
• Dosing optimal for all patients?
  • Q12 weeks is too great an interval for many patients
• Effects on comorbidities unclear
Ustekinumab
IL-12/23 Blocker

Who gets this drug:

- Any patient with moderate-to-severe psoriasis
  - 1st line drug
- Patients with minimal or no psoriatic arthritis
- Pediatric (children and adolescents, off label)
- Patients who cannot self-inject
Guselkumab
IL-23 inhibitor
VOYAGE 1: Guselkumab vs adalimumab for moderate to severe psoriasis – PASI response

**PASI 75**

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUS (n=329)</td>
<td>91.2*</td>
</tr>
<tr>
<td>ADA (n=334)</td>
<td>91.2†</td>
</tr>
<tr>
<td>Placebo</td>
<td>73.1</td>
</tr>
</tbody>
</table>

**PASI 90**

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUS (n=329)</td>
<td>73.3*</td>
</tr>
<tr>
<td>ADA (n=334)</td>
<td>80.2†</td>
</tr>
<tr>
<td>Placebo</td>
<td>49.7</td>
</tr>
</tbody>
</table>

**PASI 100**

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUS (n=329)</td>
<td>37.4*</td>
</tr>
<tr>
<td>ADA (n=334)</td>
<td>44.4†</td>
</tr>
<tr>
<td>Placebo</td>
<td>17.1</td>
</tr>
</tbody>
</table>

*P<0.001 vs placebo at Week 16
†P<0.001 vs ADA at Week 24 and Week 48
Guselkumab
IL-23 Blocker

Pros

• Well tolerated and superlatively effective
• Infrequently and appropriately dosed every 2 months
• No contraindication for CHF, MS or IBD
• Low risk of TB reactivation
• Likely very effective in psoriatic arthritis
Guselkumab
IL-23 Blocker

Cons

• Effects on comorbidities unclear
• Long-term safety not fully established
Guselkumab
IL-23 Blocker

Who gets this drug:

• Any patient with moderate-to-severe psoriasis
  • 1st line drug
IL-17 inhibitors
IL-17 inhibitors: Secukinumab
Primary endpoint: P<0.0001 SKB vs placebo; blue arrows indicate peak response

P<0.05 for both SKB dosages vs ETN for Weeks 3–12, and at Week 2 for SKB 300 mg vs ETN. Only P-values at Week 12 were adjusted for multiplicity

Data presented for number of evaluable patients

CLEAR: Secukinumab vs ustekinumab at 1 year – PASI 90 response

- 52-week head-to-head, randomized, double-blind comparator trial

*P<0.05; †P≤0.001 vs UST

Missing data were calculated using multiple imputation. NRI analysis at Week 52: 74.9% vs 60.6% (P=0.0001)

IL-17 inhibitors: Ixekizumab
UNCOVER-3: Response rates with continuous ixekizumab treatment for 60 weeks

Nonresponder imputation

\(^a\)N=385 for induction period; \(^b\)N=386 for induction period

IXORA-S: Ixekizumab vs ustekinumab: PASI 90 and PASI 100

**PASI 90 (NRI)**

![Graph showing PASI 90 results for IXE and UST.](image)

**PASI 100 (NRI)**

![Graph showing PASI 100 results for IXE and UST.](image)

*P<0.001, by Fisher's exact test

Reich K, et al. AAD 2017, Late-breaking Research: Clinical Trials, 5174
IL-17 inhibitors: Brodalumab
AMAGINE-1: PASI response rates with brodalumab at Week 12

All primary and secondary endpoints met

- **BRO 140 mg q2w (n=219)**
- **BRO 210 mg q2w (n=222)**
- **Placebo (n=220)**

- **PASI 75**: 60.3%, 83.3%, 2.7%
- **PASI 90**: 42.5%, 70.3%, 0.5%
- **PASI 100**: 23.3%, 41.9%, 0.9%

Patients with an inadequate response (sPGA ≥3 or persistent sPGA ≥2 for at least 4 weeks) at or after Week 16 were imputed as nonresponders for subsequent weeks up to Week 52; NRI was used to impute missing data.

Integrated AMAGINE-2 and -3: PASI 100 response up to Week 52 for brodalumab

![Graph showing PASI 100 response up to Week 52 for brodalumab.]

Patients with an inadequate response (sPGA ≥3 or persistent sPGA ≥2 for at least 4 weeks) at or after Week 16 were imputed as nonresponders for subsequent weeks up to Week 52; NRI was used to impute missing data.

### Brodalumab Phase 2 and 3 studies (cross indication): Suicidal ideation and behavior AEs through end of study

<table>
<thead>
<tr>
<th></th>
<th>Psoriasis N=4464 Pt-y = 9161.8</th>
<th>Asthma N=434 Pt-y=165</th>
<th>Crohn’s disease N=116 Pt-y=33.6</th>
<th>PsA N=991 Pt-y=920.2</th>
<th>RA N=238 Pt-y=157.6</th>
<th>Total N=6243 Pt-y=10,438</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicidal ideation and behavior event</td>
<td>34 (0.37)</td>
<td>0</td>
<td>0</td>
<td>3 (0.33)</td>
<td>2 (1.27)</td>
<td>39 (0.37)</td>
</tr>
<tr>
<td>Suicidal behavior</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed suicide</td>
<td>15 (0.16)</td>
<td>0</td>
<td>0</td>
<td>1 (0.11)</td>
<td>2 (1.27)</td>
<td>18 (0.17)</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>22 (0.24)</td>
<td>0</td>
<td>0</td>
<td>2 (0.22)</td>
<td>0</td>
<td>24 (0.23)</td>
</tr>
</tbody>
</table>
IL-17 inhibitors

Pros

• Well tolerated and superlatively effective
• No contraindication in CHF or MS
• Low risk of TB reactivation
• Effective for psoriatic arthritis
IL-17 inhibitors

Cons

• Dosing optimal for all patients?
  • Every month may be too infrequent for secukinumab and ixekizumab (after week 13 step down); brodalumab has most optimal dosing schedule at every 2 weeks
  • Some fall-off in efficacy for heavier patients

• Contraindicated in IBD

• Ixekizumab often has painful injections and some hypersensitivity reactions

• Secukinumab requires 2 injections per dose, yet injections are painless

• REMS program with make brodalumab will be the most challenging to prescribe

• Effects on comorbidities unclear
IL-17 inhibitors

Who gets these drugs:

- Any patient with moderate-to-severe psoriasis
  - secukinumab and ixekizumab are 1st line drugs
  - brodalumab will be used in patients who have failed other medications, and likely, more than one MOA

- Patients with psoriatic arthritis
Apremilast
PDE4 inhibitor
ESTEEM 2: Week 16 efficacy data

- 16-week results from Phase 3 ESTEEM 2 study mirror those of ESTEEM 1

**ESTEEM 1:** PASI 75 by prior treatment at Week 16 (LOCF, full analysis set; N=844)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Apremilast 30 mg bid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>5.3</td>
<td>33.1</td>
</tr>
<tr>
<td>No prior systemic</td>
<td>7.6</td>
<td>38.7</td>
</tr>
<tr>
<td>No prior biologic</td>
<td>5.9</td>
<td>35.8</td>
</tr>
<tr>
<td>Prior biologic</td>
<td>3.8</td>
<td>26.5</td>
</tr>
<tr>
<td>Failed prior TNFi</td>
<td>0</td>
<td>26.9</td>
</tr>
</tbody>
</table>

**ESTEEM 2:** PASI 75 by prior treatment at Week 16 (LOCF, full analysis set; N=411)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Apremilast 30 mg bid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>5.8</td>
<td>28.8</td>
</tr>
<tr>
<td>No prior systemic</td>
<td>3.6</td>
<td>33.3</td>
</tr>
<tr>
<td>No prior biologic</td>
<td>6.5</td>
<td>31.9</td>
</tr>
<tr>
<td>Prior biologic</td>
<td>4.5</td>
<td>22.8</td>
</tr>
<tr>
<td>Failed prior TNFi</td>
<td>10</td>
<td>23.5</td>
</tr>
</tbody>
</table>

*P<0.0001; †P=0.0273 vs PBO; aConventional ± biologics.

Paul C, et al. AAD 2014, P8412; Reich K, et al. AAD 2013, Late breaker
Apremilast
PDE4 Blocker

Pros

• Oral medication
• No monitoring requirements
• No contraindication in CHF, MS or IBD
• Low risk of TB reactivation
• Weight loss might be a positive
Apremilast
PDE4 Blocker

Cons

• Low efficacy for both skin and arthritis
• Effects on comorbidities unclear
• Poor tolerability in some patients
  • Diarrhea, nausea
• Rare mood disorders (depression)
• Weight loss might be a negative
Who gets this drug:

- Any patient with moderate-to-severe psoriasis
- Patients who fail higher efficacy biologics
  - I have a preference for higher efficacy biologic therapies
- No ability to self-inject and stronger preference for oral medication
Key Points

- Choose therapy based on individual patient characteristics
- Ps treatment is NOT stepwise (i.e. not required to fail on topicals)
- One drug or modality may succeed when others fail
- Combination therapy may be desirable in some patients
Thank you

Bruce E. Strober, MD, PhD
strober@uchc.edu